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Mazzolini et al.

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(45) **Date of Patent: Nov. 16, 2021**

(54) **COMPOSITIONS AND METHODS FOR INCREASING MESENCHYMAL STROMAL CELL MIGRATION TO TUMORS**

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Related U.S. Application Data

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(51) **Int. Cl.**

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C12N 5/077	(2010.01)
C12N 5/0775	(2010.01)

(52) **U.S. Cl.**

CPC ***A61K 35/28*** (2013.01); ***C12N 5/0668*** (2013.01); ***C12N 5/0669*** (2013.01); *C12N 2501/20* (2013.01); *C12N 2501/40* (2013.01); *C12N 2501/998* (2013.01); *C12N 2502/99* (2013.01)

(58) **Field of Classification Search**

CPC A61K 35/28; C12N 5/0669; C12N 5/0668; C12N 2502/99; A61P 35/00

See application file for complete search history.

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(57) **ABSTRACT**

The present application is directed to compositions and methods for treating a subject with cancer and/or increasing migration of a mesenchymal stromal cells (MSCs) stimulated with a recombinant autocrine motility factor (rAMF) to a tumor or a tumor cell, e.g. hepatocellular carcinoma (HCC). In addition, methods for increasing adhesion of MSCs to endothelial cells with rAMF are disclosed. In some embodiments, the MSCs comprise a therapeutic agent, e.g., an anti-tumor agent.

19 Claims, 11 Drawing Sheets

Specification includes a Sequence Listing.

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FIG. 1A-B

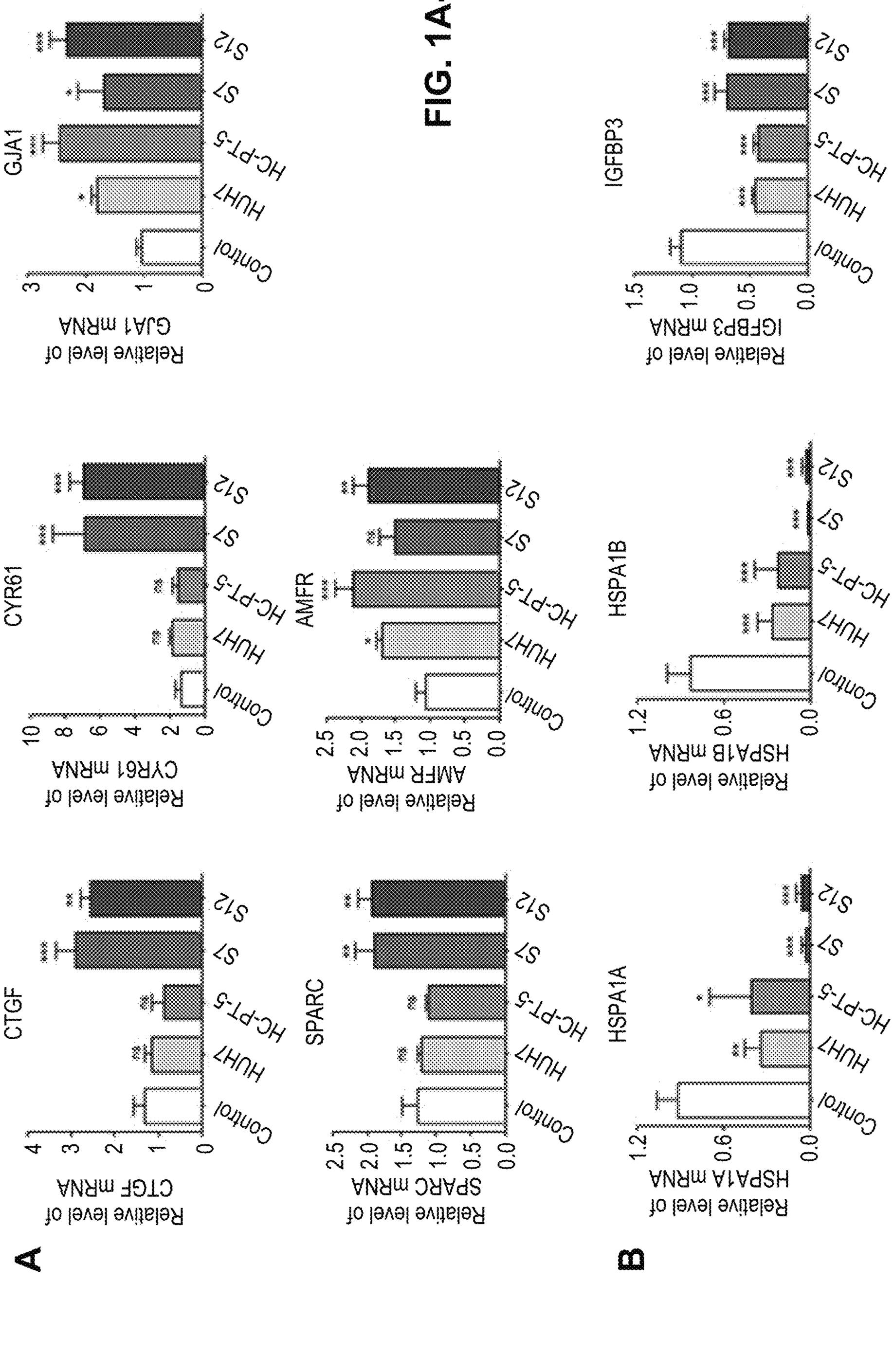
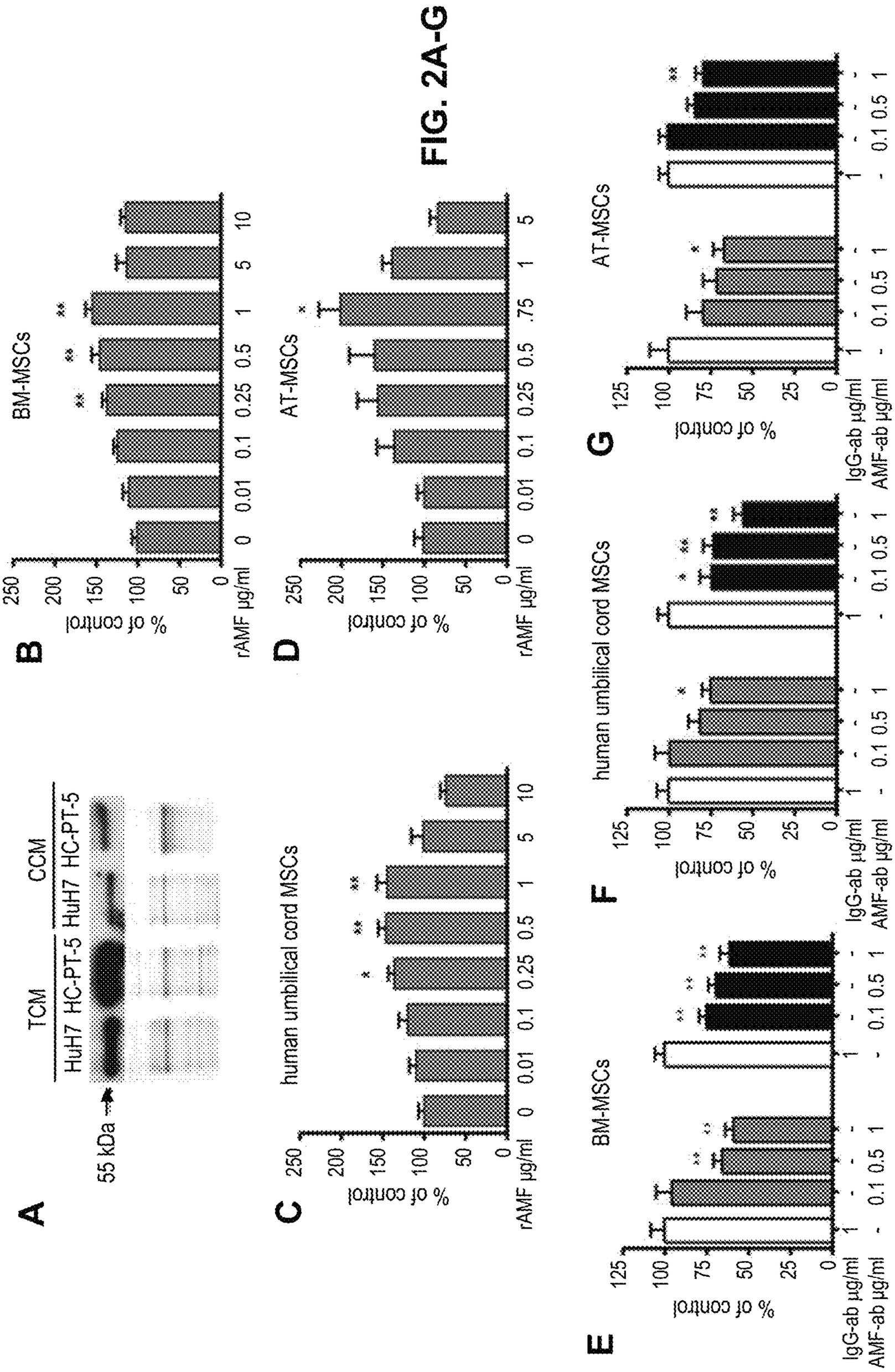

A
B
GJA1
Relative level of GJA1 mRNA
IGFBP3
Relative level of IGFBP3 mRNA
CYR61
Relative level of CYR61 mRNA
AMFR
Relative level of AMFR mRNA
HSPA1B
Relative level of HSPA1B mRNA
CTGF
Relative level of CTGF mRNA
SPARC
Relative level of SPARC mRNA
HSPA1A
Relative level of HSPA1A mRNA
Control
HUH7
HC-PT-5
S7
S12

FIG. 2A-G


A
TCM
HuH7 HC-PT-5 HuH7 HC-PT-5
55 kDa
B
BM-MSCs
% of control
rAMF µg/ml 0 0.01 0.1 0.25 0.5
C
human umbilical cord MSCs
% of control
rAMF µg/ml 0 0.01 0.1 0.25 0.5
D
AT-MSCs
% of control
rAMF µg/ml 0 0.01 0.1 0.25 0.5
E
BM-MSCs
% of control
IgG-ab µg/ml 1 - - - 1 - - -
AMF-ab µg/ml - 0.1 0.5 1 - 0.1 0.5 1
F
human umbilical cord MSCs
% of control
IgG-ab µg/ml 1 - - - 1 - - -
AMF-ab µg/ml - 0.1 0.5 1 - 0.1 0.5 1
G
AT-MSCs
% of control
IgG-ab µg/ml 1 - - - 1 - - -
AMF-ab µg/ml - 0.1 0.5 1 - 0.1 0.5 1

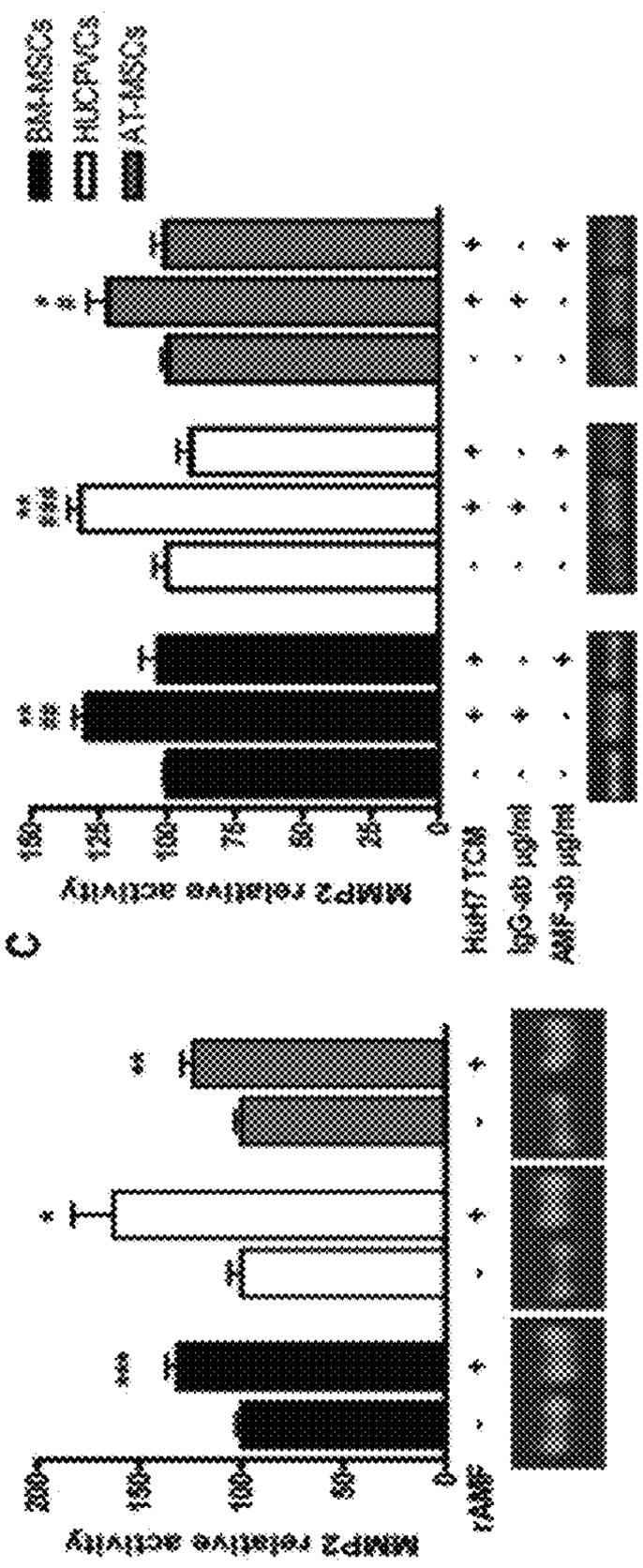

BM-MSCs
HUC-MSCs
AT-MSCs
MMP2 relative activity
rAMF
C
Huh7 TCM
IgG-ab μg/ml
AMF-ab μg/ml
MMP2 relative activity
B
MMP2 fold change ($2^{-\Delta\Delta CT}$)
A
BM-MSCs
BM-MSCs-rAMF
% invasion
Phe mM
Huh7 TCM
HC-PT-5 TCM
D

FIG. 3A-D

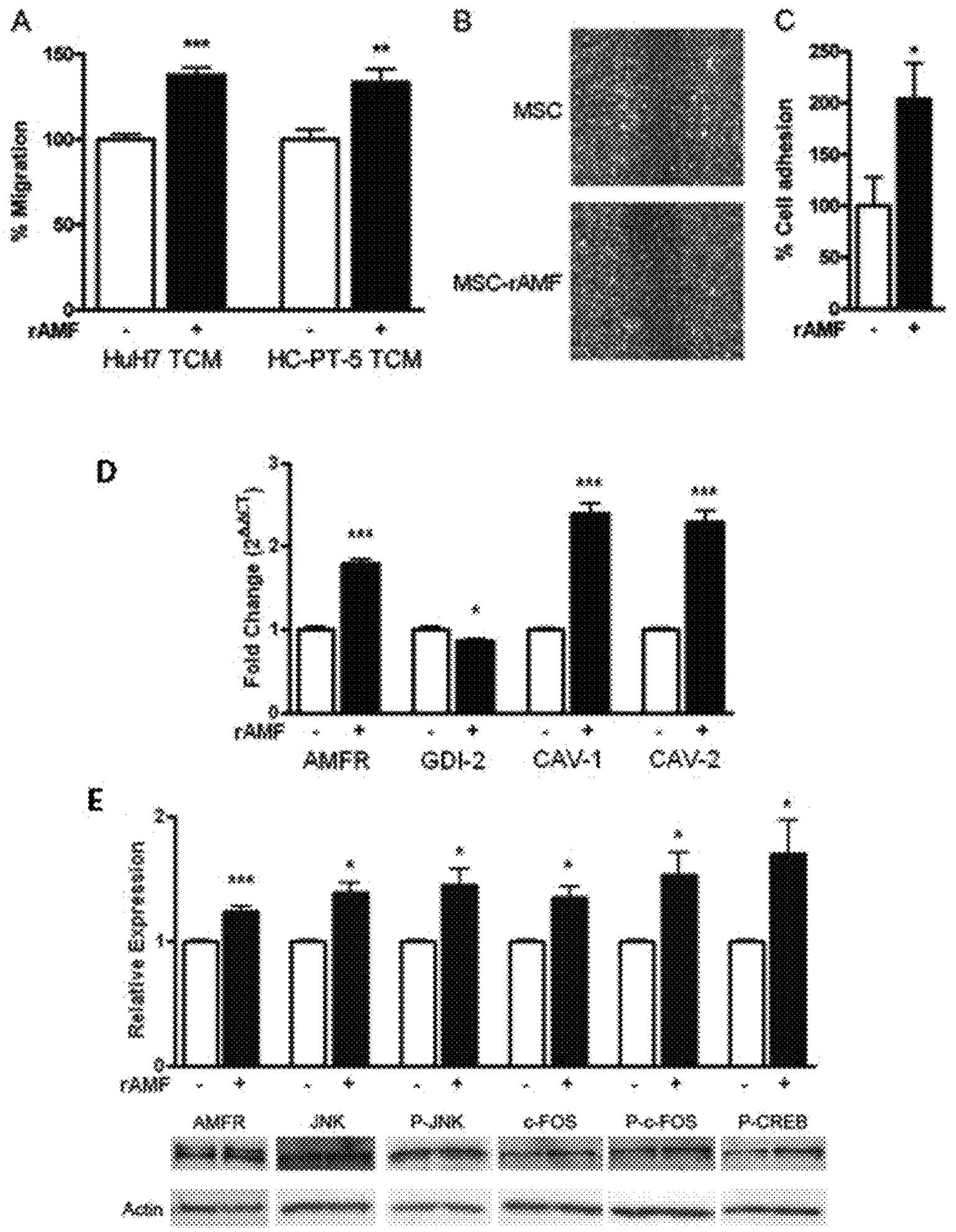

A
% Migration
rAMF
HuH7 TCM
HC-PT-5 TCM
B
MSC
MSC-rAMF
C
% Cell adhesion
rAMF
D
Fold Change (2^-ΔΔCT)
rAMF
AMFR
GDI-2
CAV-1
CAV-2
E
Relative Expression
rAMF
AMFR
JNK
P-JNK
c-FOS
P-c-FOS
P-CREB
Actin

FIG. 4A-E

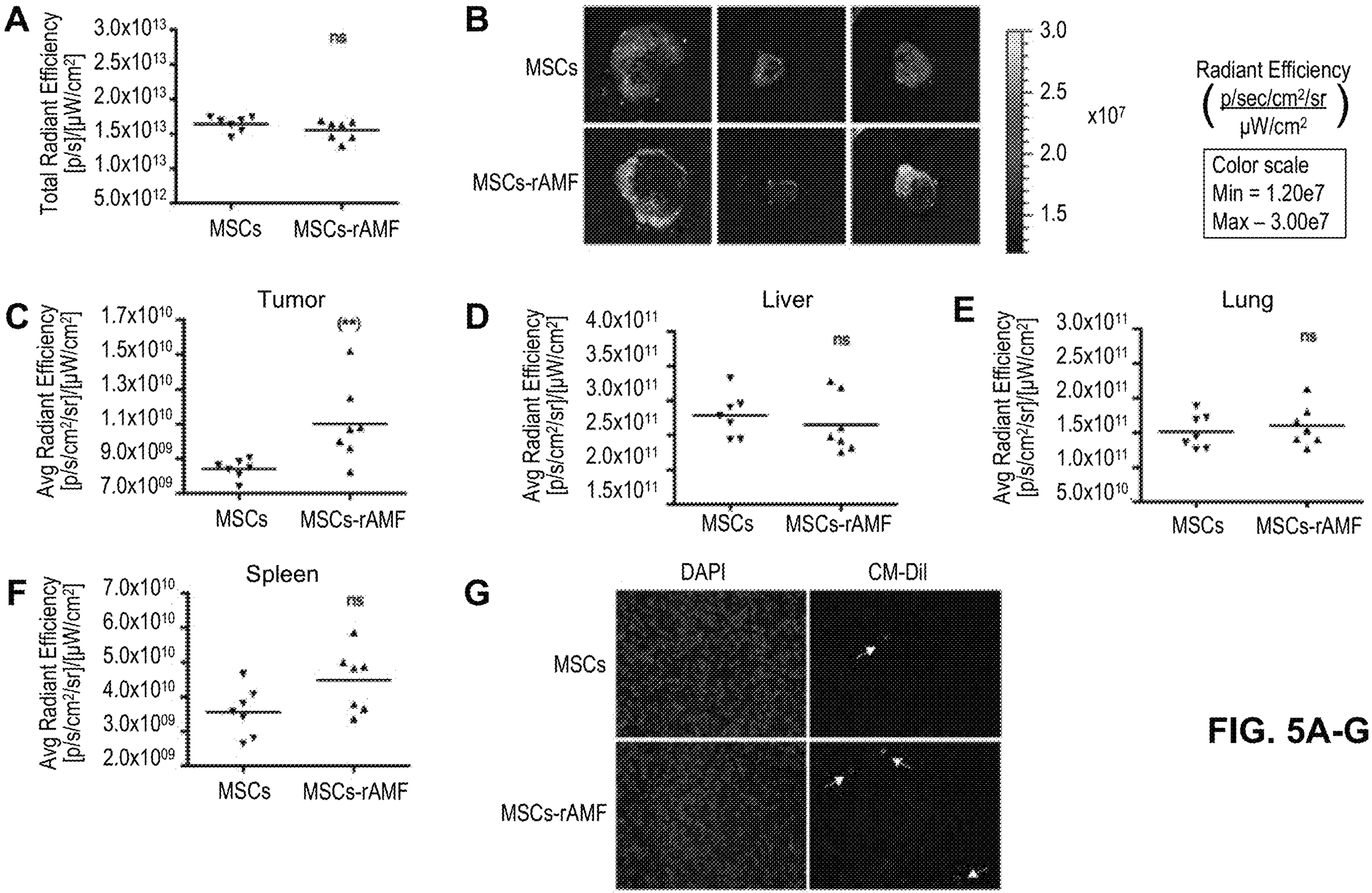

A
Total Radiant Efficiency [p/s]/[μW/cm²]
3.0x10¹³
2.5x10¹³
2.0x10¹³
1.5x10¹³
1.0x10¹³
5.0x10¹²
ns
MSCs
MSCs-rAMF
B
MSCs
MSCs-rAMF
3.0
2.5
2.0
1.5
x10⁷
Radiant Efficiency (p/sec/cm²/sr / μW/cm²)
Color scale
Min = 1.20e7
Max – 3.00e7
C
Tumor
Avg Radiant Efficiency [p/s/cm²/sr]/[μW/cm²]
1.7x10¹⁰
1.5x10¹⁰
1.3x10¹⁰
1.1x10¹⁰
9.0x10⁰⁹
7.0x10⁰⁹
(**)
MSCs
MSCs-rAMF
D
Liver
Avg Radiant Efficiency [p/s/cm²/sr]/[μW/cm²]
4.0x10¹¹
3.5x10¹¹
3.0x10¹¹
2.5x10¹¹
2.0x10¹¹
1.5x10¹¹
ns
MSCs
MSCs-rAMF
E
Lung
Avg Radiant Efficiency [p/s/cm²/sr]/[μW/cm²]
3.0x10¹¹
2.5x10¹¹
2.0x10¹¹
1.5x10¹¹
1.0x10¹¹
5.0x10¹⁰
ns
MSCs
MSCs-rAMF
F
Spleen
Avg Radiant Efficiency [p/s/cm²/sr]/[μW/cm²]
7.0x10¹⁰
6.0x10¹⁰
5.0x10¹⁰
4.0x10¹⁰
3.0x10⁰⁹
2.0x10⁰⁹
ns
MSCs
MSCs-rAMF
G
DAPI
CM-DiI
MSCs
MSCs-rAMF

FIG. 5A-G

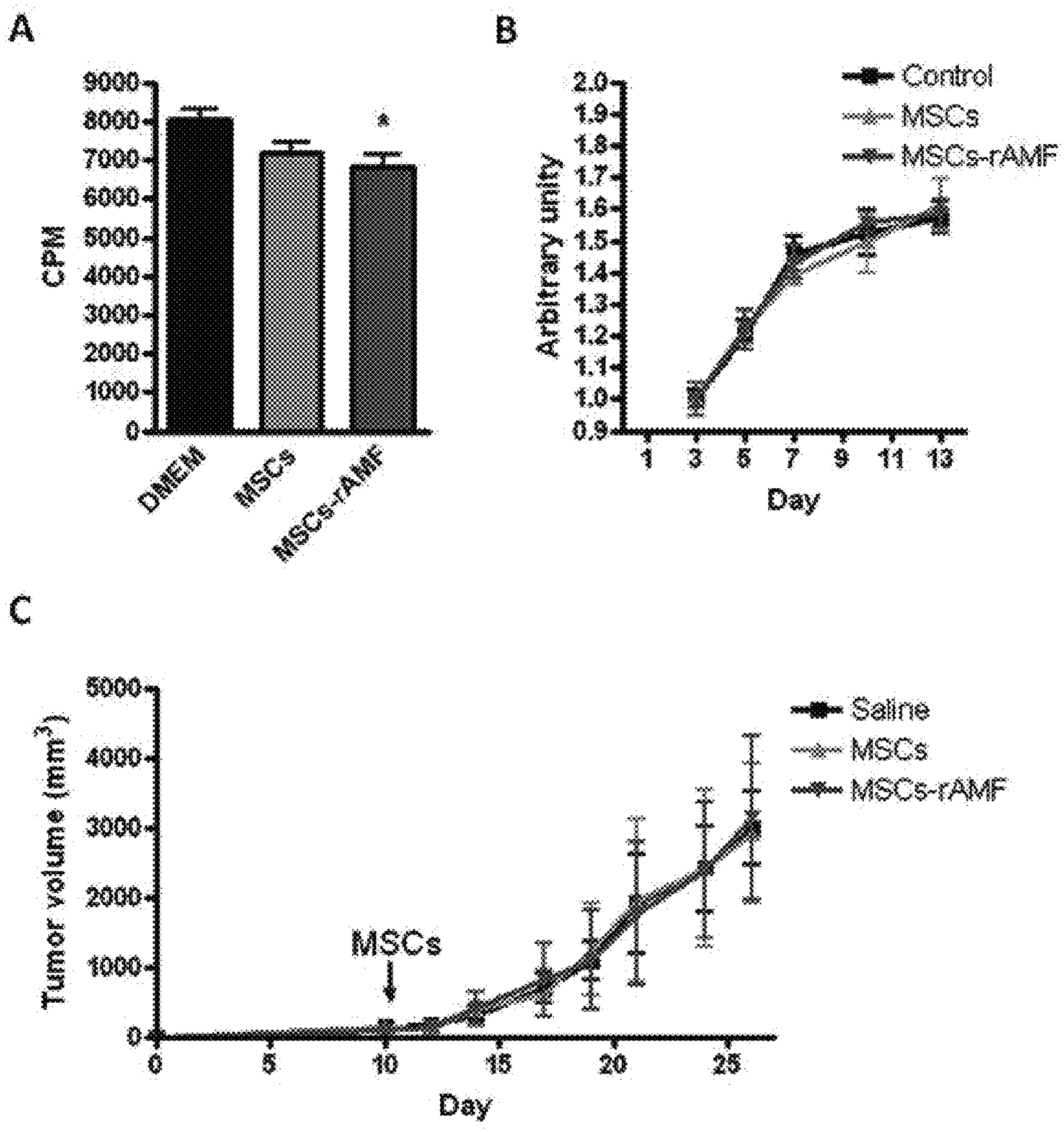

A
CPM
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
*
DMEM
MSCs
MSCs-rAMF
B
Arbitrary unity
2.0
1.9
1.8
1.7
1.6
1.5
1.4
1.3
1.2
1.1
1.0
0.9
1
3
5
7
9
11
13
Day
Control
MSCs
MSCs-rAMF
C
Tumor volume (mm3)
5000
4000
3000
2000
1000
0
MSCs
0
5
10
15
20
25
Day
Saline
MSCs
MSCs-rAMF

FIG. 6A-C

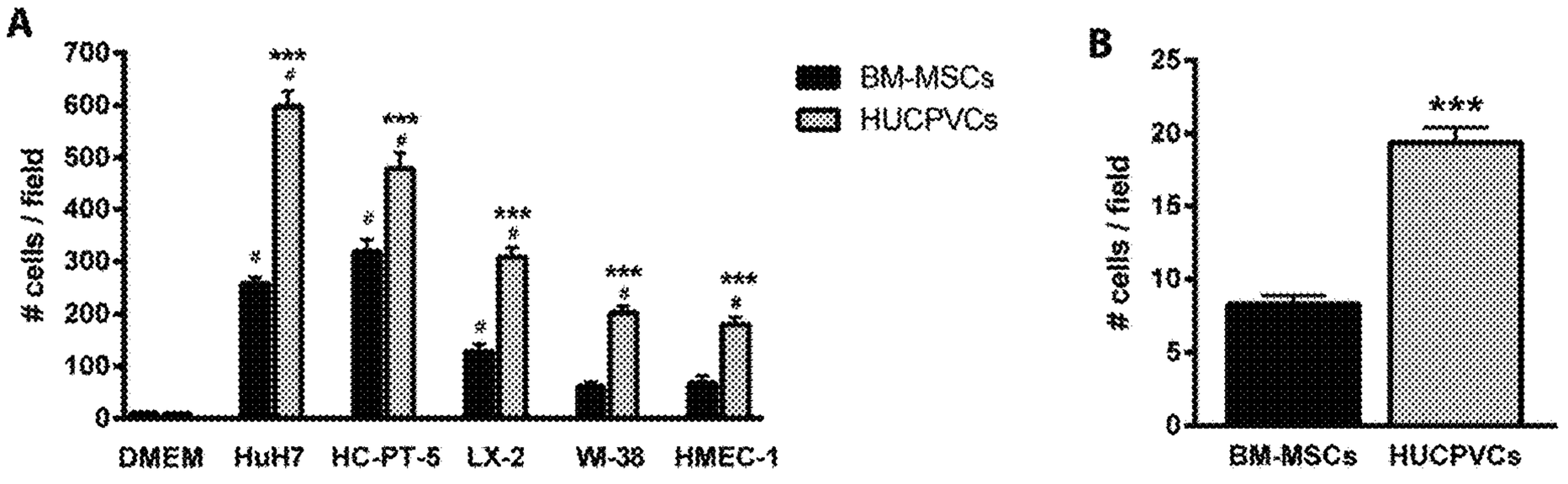

A
cells / field
700
600
500
400
300
200
100
0
DMEM
HuH7
HC-PT-5
LX-2
WI-38
HMEC-1
BM-MSCs
HUCPVCs
B
cells / field
25
20
15
10
5
0
BM-MSCs
HUCPVCs

FIG. 7A-B

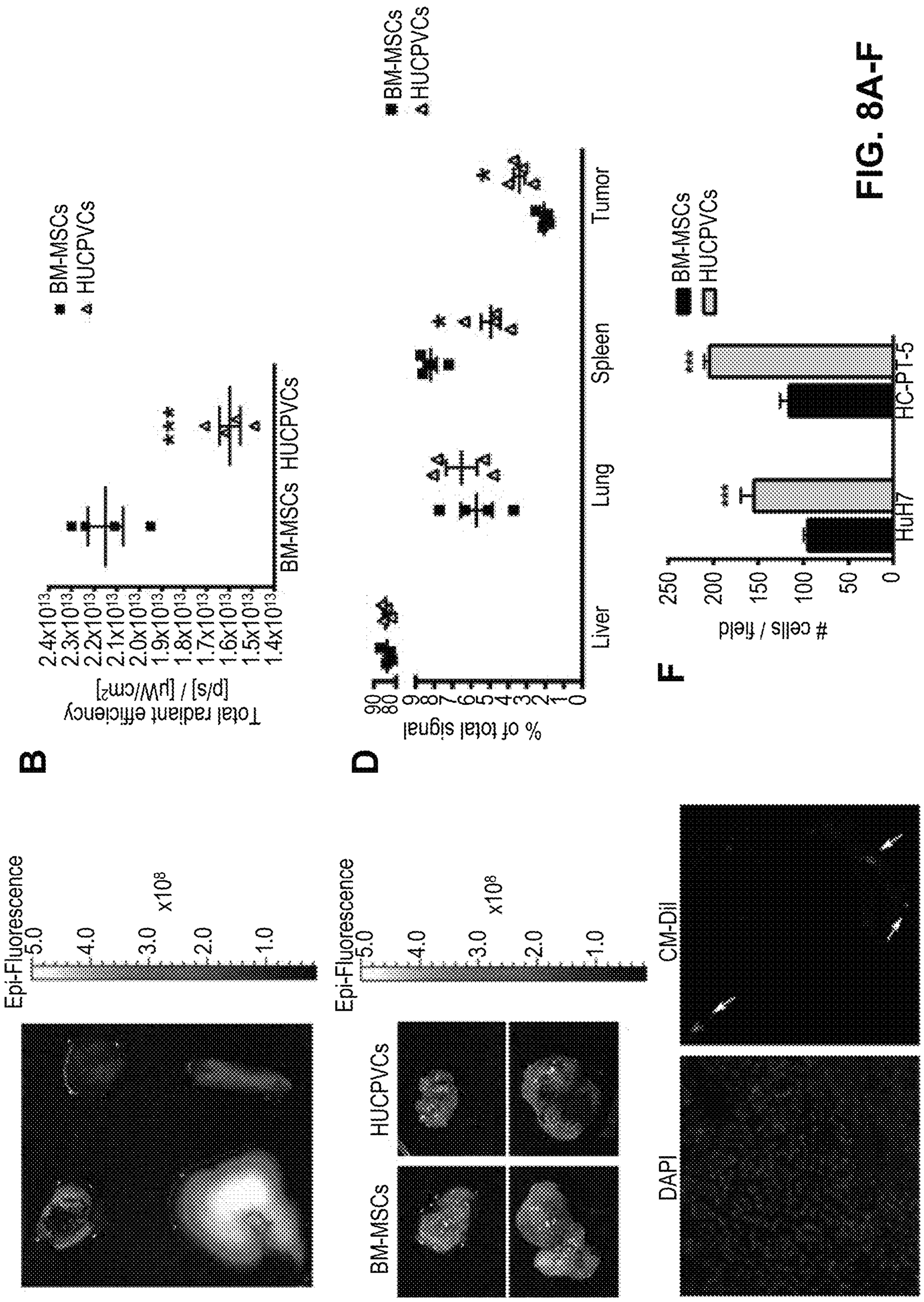

A
Epi-Fluorescence
5.0
4.0
3.0
2.0
1.0
x10^8
B
Total radiant efficiency
[p/s] / [μW/cm²]
2.4x10^13
2.3x10^13
2.2x10^13
2.1x10^13
2.0x10^13
1.9x10^13
1.8x10^13
1.7x10^13
1.6x10^13
1.5x10^13
1.4x10^13
BM-MSCs
HUCPVCs
***
C
BM-MSCs
HUCPVCs
Epi-Fluorescence
5.0
4.0
3.0
2.0
1.0
x10^8
D
% of total signal
90
80
70
60
50
40
30
20
10
0
Liver
Lung
Spleen
Tumor
BM-MSCs
HUCPVCs
E
DAPI
CM-DiI
F
cells / field
250
200
150
100
50
0
***
***
HuH7
HC-PT-5
BM-MSCs
HUCPVCs

FIG. 8A-F

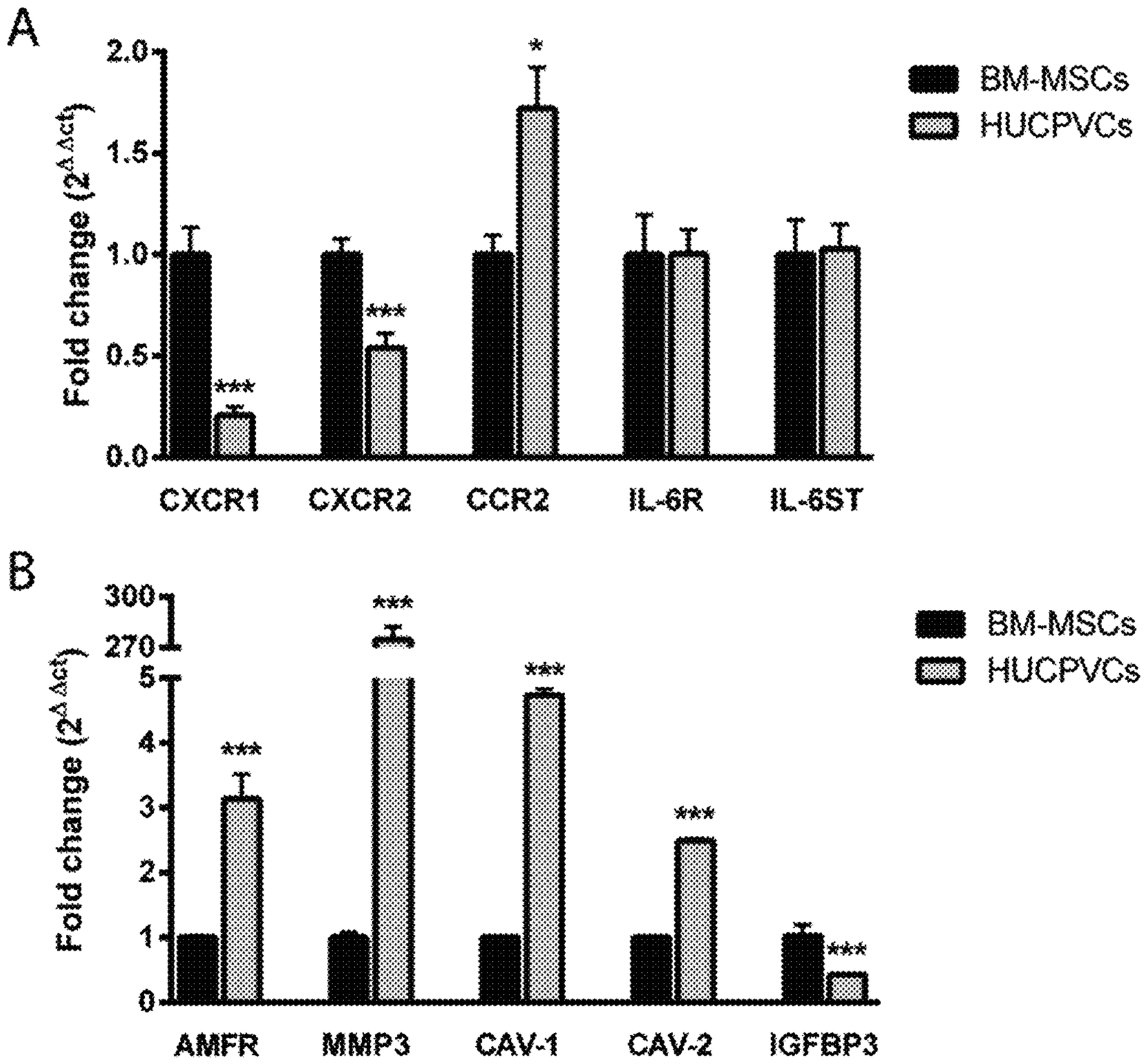

A
Fold change ($2^{\Delta\Delta ct}$)
2.0
1.5
1.0
0.5
0.0
***
***
*
BM-MSCs
HUCPVCs
CXCR1
CXCR2
CCR2
IL-6R
IL-6ST
B
Fold change ($2^{\Delta\Delta ct}$)
300
270
5
4
3
2
1
0
***
***
***
***
***
BM-MSCs
HUCPVCs
AMFR
MMP3
CAV-1
CAV-2
IGFBP3

FIG. 9A-B

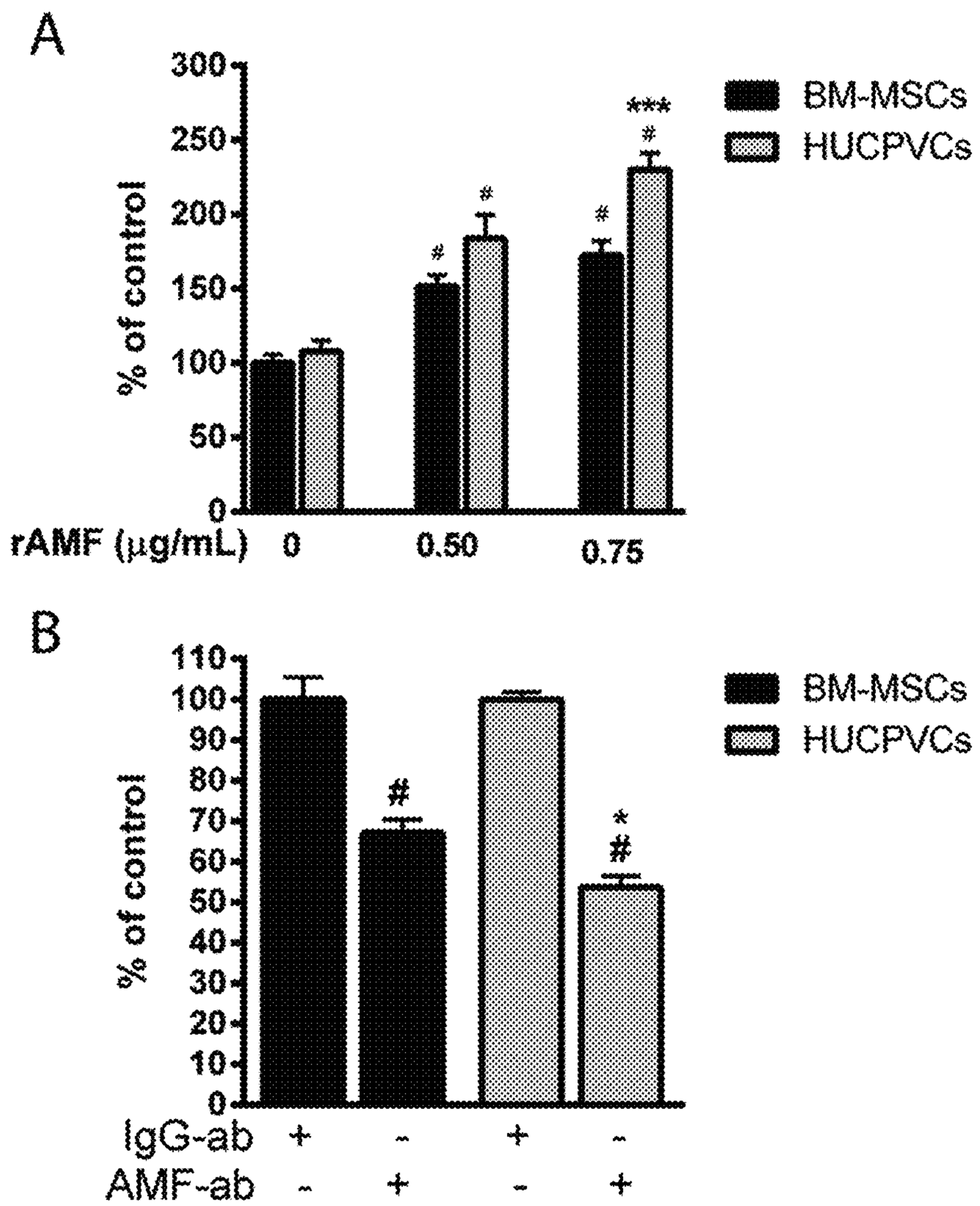

A
300
250
200
150
100
50
0
% of control
BM-MSCs
HUCPVCs
***
#
rAMF (μg/mL) 0 0.50 0.75
B
110
100
90
80
70
60
50
40
30
20
10
0
% of control
BM-MSCs
HUCPVCs
*
IgG-ab + - + -
AMF-ab - + - +

FIG. 10A-B

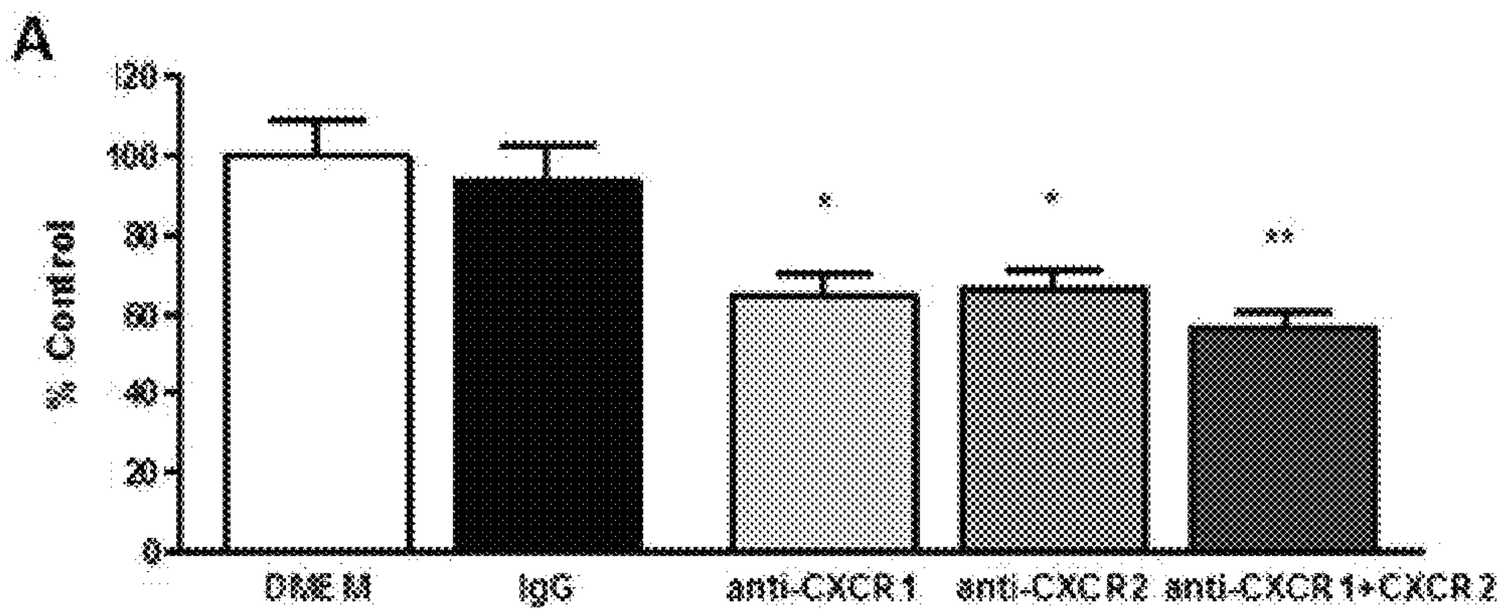

A
% Control
120
100
80
60
40
20
0
*
*
**
DMEM
IgG
anti-CXCR1
anti-CXCR2
anti-CXCR1+CXCR2
B
% Control
120
100
80
60
40
20
0
*
DMEM
anti-HGF
anti-MCP-1

FIG. 11A-B

COMPOSITIONS AND METHODS FOR INCREASING MESENCHYMAL STROMAL CELL MIGRATION TO TUMORS

REFERENCE TO SEQUENCE LISTING SUBMITTED ELECTRONICALLY

The content of the electronically submitted sequence listing in ASCII text file (Name: "3181_0060002_Sequence_Listing_ST25.txt"; Size: 10,719; and Date of Creation: Feb. 7, 2018) filed with the application is incorporated herein by reference in its entirety.

BACKGROUND

Mesenchymal stromal cells (MSCs) (also referred to as fibroblastic colony forming units or mesenchymal stem cells) constitute a heterogeneous cell population, characterized by their adherence to plastic, fibroblast-like morphology, expression of specific markers (e.g., CD105+, CD90+, CD73+), lack of hematopoietic markers (e.g., CD45, CD34, CD14 or CD11b, CD79a or CD19) and HLA class II and capability to differentiate in vitro into osteoblasts, adipocytes and chondroblasts (Dominici, M., K. Le Blanc, et al. (2006) Cytotherapy 8(4): 315-317). MSCs are most often derived from bone marrow (BM), but can also be isolated from adipose tissue (AT) or from umbilical cord; from the latter case, MSC are isolated from the Wharton's jelly (WJ-MSCs), perivascular areas (mesenchymal cells harvested from umbilical cord perivascular tissue) or umbilical cord blood (CB-MSCs) (Bernardo, M. E., F. Locatelli, et al. (2009) Ann N Y Acad Sci 1176: 101-117). MSCs show tropism for inflamed, injured or tumorigenic sites and their ability to be cultured and expanded in vitro, their self-renewal properties and low immunogenicity make these cells useful for cell therapy (Prockop, D. J. and J. Y. Oh (2012) J Cell Biochem 113(5): 1460-1469). However, the mechanisms involved in MSCs recruitment to tumors in general, and to specific tumors, e.g., hepatocellular carcinoma (HCC), are not fully understood.

Autocrine motility factor (AMF) is a 55-kDa cytokine (SEQ ID NO:1) secreted by tumors that regulates cell motility (Liotta, L. A., R. Mandler, et al. (1986) Proc Natl Acad Sci USA 83(10): 3302-3306). AMF was isolated, purified, and partially characterized from the serum-free conditioned medium of human A2058 melanoma cells (Liotta, L. A., R. Mandler, et al. (1986)). AMF exhibits sequence identity with glucose-6-phosphate isomerase (GPI) (alternatively known as phosphoglucose isomerase or phosphohexose isomerase (PHI)), a glycolytic enzyme involved in carbohydrate metabolism (Watanabe, H., K. Takehana, et al. (1996) Cancer Res 56(13): 2960-2963). The stimulation of cell motility is induced by the binding to the autocrine motility factor receptor (AMFR), a 78-kDa seven transmembrane glycoprotein with leucine zipper and RING-H2 motifs (Shimizu, K., M. Tani, et al. (1999) FEBS Lett 456(2): 295-300). AMFR is stably localized in caveolae, and caveolin-1 (Cav-1) has the ability to regulate the endocytic pathway through the stabilization of caveolae expression (Le, P. U., G. Guay, et al. (2002) J Biol Chem 277(5): 3371-3379).

AMF is secreted by different tumors such as lung (Dobashi, Y., H. Watanabe, et al. (2006) J Pathol 210(4): 431-440), gastrointestinal, kidney and mammary (Baumann, M., A. Kappl, et al. (1990) Cancer Invest 8(3-4): 351-356) as well as by hepatocellular carcinomas (Torimura, T., T. Ueno, et al. (2001) Hepatology 34(1): 62-71). Migration of hepatocellular carcinoma cells upon AMF stimulation has been associated to upregulation of metalloproteinase 3 (MMP3) (Yu, F. L., M. H. Liao, et al. (2004) Biochem Biophys Res Commun 314(1): 76-82) and activation of the small G-protein RhoC (Yanagawa, T., H. Watanabe, et al. (2004) Lab Invest 84(4): 513-522).

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and the third cause of cancer-related death (Ferenci, P., M. Fried, et al. (2010) J Gastrointestin Liver Dis 19(3): 311-317). Most cases of HCC are secondary to either a viral hepatitis infection (hepatitis B or C) or cirrhosis. Curative therapies such as resection or liver transplantation have been demonstrated to improve patient survival (de Lope, C. R., S. Tremosini, et al. (2012) J Hepatol 56 Suppl 1: S75-87); however, these strategies can only be applied to a minority of patients. Therefore, there is an urgent therapeutic need for patients with HCC.

BRIEF SUMMARY

The present application relates to the combined use of cellular and gene therapy to deliver therapeutic genes, e.g., an anti-tumor agent, into tumoral or peritumoral tissues. In some embodiments, the application relates to compositions and methods for treating a subject with cancer and/or increasing migration of a mesenchymal stromal cells (MSCs) to a tumor or a tumor cell, e.g. hepatocellular carcinoma (HCC), wherein the MSC comprises a therapeutic agent, e.g., an anti-tumor agent, and is stimulated with a recombinant autocrine motility factor (rAMF). In addition, methods for increasing adhesion of MSCs to endothelial cells with rAMF are disclosed.

BRIEF DESCRIPTION OF THE DRAWINGS/FIGURES

FIG. **1**A-B. Shows real-time PCR (RT-PCR) relative expression of (A) up-regulated and (B) down-regulated genes in MSCs exposed to tumor conditioned media (TCM).

FIG. **2**A-G. Shows (A) detection of AMF (55 kDa) by Western blot in CCM derived from HCC cells and TCM from ex vivo HCC s.c. tumors (upper panel). Colloidal Coomassie staining was performed as loading control (lower panel). MSCs migration was analyzed using Boyden chamber assays with rAMF as chemoattractant for (B) BM-MSCs, (C) Mesenchymal cells harvested from umbilical cord perivascular tissue or (D) AT-MSCs. Results are expressed as percentage of control (DMEM) SEM. *$p<0.05$ and **$p<0.01$ vs DMEM (ANOVA and Dunnett's test). Cell migration of (E) BM-MSCs, (F) Mesenchymal cells harvested from umbilical cord perivascular tissue or (G) AT-MSCs towards TCM derived from HuH7 (gray bars) or HC-PT-5 (black bars) pretreated with anti-AMF-Ab (AMF-ab) or control isotype IgG (IgG-ab) is shown. Results are expressed as percentage of control (isotype control) SEM. *$p<0.05$ and **$p<0.01$ vs isotype control (ANOVA and Dunnett's comparison test). Results are representative of 3 independent experiments.

FIG. **3**A-D. Shows (A) MMP3 expression determined by qRT-PCR in BM-MSCs (black bars), Mesenchymal cells harvested from umbilical cord perivascular tissue (white bars) or AT-MSCs (gray bars) stimulated with 1 μg/ml of rAMF. ** $p<0.01$ vs unstimulated cells (DMEM, unpaired Student's t test). (B) MMP2 activity evaluated by zymography in supernatants of BM-MSCs (black bars), Mesenchymal cells harvested from umbilical cord perivascular tissue (white bars) or AT-MSCs (gray bars) pre-stimulated

with 1 μg/mL of rAMF. Band intensity of 3 independent experiments was detected by densitometric evaluation and plotted as MMP2 relative activity. One representative image of the zymography is shown. * $p<0.05$, ** $p<0.01$ and *** $p<0.001$ vs untreated cells (DMEM, ANOVA and Tukey's comparison test). (C) MMP2 activity was evaluated by zymography in MSCs (BM-MSCs, black bars; Mesenchymal cells harvested from umbilical cord perivascular tissue, white bars; and AT-MSCs, gray bars) culture supernatant stimulated with TCM from HuH7 cells. TCM from HuH7 cells was blocked with anti-AMF (AMF-ab) or isotype control (IgG-ab). Band intensity of 3 independent experiments was detected by densitometric evaluation and plotted as MMP2 relative activity. One representative image of the zymography is shown. * $p<0.05$ and ** $p<0.01$ vs DMEM (ANOVA); # $p<0.05$, ## $p<0.01$ and ### $p<0.001$ vs AMF-blocked TCM from HuH7 (HuH7 TCM+/AMF-ab+, ANOVA and Tukey's comparison test). (D) Invasion capacity of untreated BM-MSCs (white bars) or BM-MSCs stimulated with rAMF (black bars) to type IV collagen using TCM from HuH7 or HC-PT-5 preincubated with different doses of the MMP inhibitor 1,10 phenantroline (Phe). *** $p<0.001$ vs without stimulation with rAMF and aaa $p<0.001$ vs without preincubation with Phe (ANOVA). Results are representative of 3 independent experiments.

FIG. **4**A-E. Shows (A) pretreatment of BM-MSCs with 1 μg/mL rAMF (black bars) increases chemotaxis towards TCM derived from HuH7 or HC-PT-5 cells compared to untreated cells (white bars). (B) Shows a wound-healing assay of MSCs after pretreatment with rAMF or control (DMEM). Representative images were taken 24 hours after scratching. (C) Adhesion to HMEC-1 endothelial cells was increased in BM-MSCs exposed to rAMF. (D) Shows expression of AMF receptor (AMFR), GDP dissociation inhibitor 2 (GDI-1), caveolin-1 (CAV-1) and caveolin-2 (CAV-2) by qRT-PCR. * $p<0.05$, ** $p<0.01$ and *** $p<0.001$ vs untreated cells (DMEM, white bars, unpaired Student's t-test. (E) Shows increased expression of AMFR, JNK, p-JNK, c-Fos, p-c-Fos and p-CREB in AMF-treated MSCs evaluated by western blot.

FIG. **5**A-G. BM-MSCs pre-stimulated with Ig/ml of rAMF were labeled with DiR and CMDiI cell trackers and i.v. injected in s.c. HuH7 tumor-bearing mice. After 3 days, tumors were removed and fluorescence imaging (FI) was performed. (A) Shows total fluorescent intensity as calculated by measuring the region of interest (ROI) for all the tissues isolated and the results were expressed as total radiant efficiency. ns, non significant. (B) Shows representative tumors images of mice inoculated with rAMF-prestimulated BM-MSCs (MSC-rAMF) or unstimulated cells (MSCs). Images represent the average radiant efficiency. Region of interest (ROI) was calculated for the isolated (C) tumor, (D) liver, (E) lung and (F) spleen and the results were expressed as the average radiant efficiency. **$p<0.01$ vs unstimulated BM-MSCs (unpaired Student's t-test). (G) Shows microscopic analysis of transplanted CM-DiI-labeled MSCs (red signal indicated by arrows) and DAPI staining in frozen sections of tumors. Magnification ×200.

FIG. **6**A-C. (A) Shows in vitro proliferation of HuH7 cells exposed to MSCs, AMF-pretreated MSCs (MSC-rAMF) or unexposed cells (DMEM). *$p<0.05$ vs DMEM (ANOVA and Tukey's comparison test). (B) Multicellular spheroid growth composed by HCC tumor cells, hepatic stellate cells and endothelial cells (control) or also by MSCs or MSCs prestimulated with rAMF (ANOVA and Tukey's comparison test). (C) In vivo tumor growth of s.c. HuH7 (saline) and also i.v. injected with MSCs or AMF-pretreated MSCs (ANOVA and Tukey's comparison test).

FIG. **7**A-B. (A) Shows in vitro migration of BM-MSCs (black bars) or HUCPVCs (grey bars) towards CCM from HCC (HuH7 and HC-PT-5), hepatic stellate cells (LX-2), fibroblasts (WI-38) or endothelial cells (HMEC-1). Bars represent the average of MSCs/field (10×) SEM from three representative visual fields. Results are representative of 3 independent experiments. # $p<0.001$ vs DMEM; *** $p<0.001$ vs BM-MSCs. (B) Adhesion towards endothelial cells of BM-MSCs (black bars) or HUCPVCs (grey bars) was measured. Results are representative of 3 independent experiments. *** $p<0.001$ vs BM-MSCs.

FIG. **8**A-F. CM-DiI and DiR pre-labeled MSCs were i.v. injected in s.c. HuH7 bearing mice. At day 3, mice were sacrificed and organs were removed: (A) lungs, livers, spleen and (C) tumors were exposed to obtain fluorescent images. Images represent the average radiant efficiency. Representative images are shown. (B) Total fluorescent intensity for injected BM-MSCs or HUCPVCs was calculated by measuring the region of interest (ROI) for all the tissues isolated and results were expressed as total radiant efficiency [p/s]/[μW/cm^2]. *** $p<0.001$. (D) Signal present in the isolated liver, spleen, lungs and tumors was represented as percentage of total signal for BM-MSCs or HUCPVCs injected mice. * $p<0.05$ vs BM-MSCs. (E) Microscopic analysis of transplanted CM-DiI-labeled MSCs (red signal indicated by arrows) and DAPI staining in frozen sections of tumors. 200× magnification. (F) In vitro migration of MSCs to TCM derived from HuH7 or HC-PT-5 s.c. tumors. Bars represent the average of MSCs/field (10×) SEM from three representative visual fields. Results are representative of 3 independent experiments. *** $p<0.001$vs BM-MSCs

FIG. **9**A-B. Expression of (A) cytokines and chemokines receptors and (B) AMF/AMFR axis proteins was evaluated in BM-MSCs (black bars) or HUCPVCs (grey bars) by qPCR. *** $p<0.001$ vs BM-MSCs.

FIG. **10**A-B. (A) In vitro migration of BM-MSCs (black bars) or HUCPVCs (grey bars) towards rAMF was measured. # $p<0.05$ vs DMEM (0 μg/ml rAMF); * $p<0.05$ vs BM-MSCs. (B) In vitro migration of BM-MSCs (black bars) or HUCPVCs (grey bars) towards HC-PT-5 TCM preincubated with anti-AMF antibody (AMF-ab) or control isotype (IgG-ab) was evaluated. # $p<0.05$ vs IgG-ab; * $p<0.05$ vs BM-MSCs. Bars represent the average of MSCs/field (10×) SEM from three representative visual fields. Results are representative of 3 independent experiments.

FIG. **11**A-B. Shows (A) Migration (% of control) towards CM-HuH7of MSCs pre-incubated with anti-CXCR1, anti-CXCR2 or both (anti-CXCR1+ anti-CXCR2) or isotype control (IgG) for 1 h. *$p<0.05$ and **$p<0.01$ vs IgG isotype control. (B) Migration (% of control) of MSCs towards CM-HuH7 pre-incubated with anti-HGF or anti-MCP-1 for 1 h. *$p<0.05$ vs DMEM. Results were expressed as percentage of control (DMEM).

DETAILED DESCRIPTION

Definitions

To facilitate an understanding of the present invention, a number of terms and phrases are defined below:

"Isolated" in regard to cells, refers to a cell that is removed from its natural environment (such as in a solid tumor) and that is isolated or separated, and is at least about 30% free, about 50% free, about 75% free, about 90% free,

about 95% free, or 100% free, from other cells with which it is naturally present, but which lack the marker based on which the cells were isolated.

As used herein, the term "heterologous" refers to, e.g., a gene, polypeptide or cell that is not in its natural environment; thus, it is non-naturally-occurring. For example, a heterologous gene or polypeptide includes a gene or polypeptide from one species introduced into another species. A heterologous gene or polypeptide also includes a gene or polypeptide native to an organism that has been altered in some way (e.g., mutated, added in multiple copies, linked to non-native regulatory sequences, etc.). In another example, a heterologous cell includes a cell native to an organism that has been altered in some way (e.g., genetically modified to include a recombinant gene, protein, or virus).

"Tumor" and "neoplasm" as used herein refer to any mass of tissue that results from excessive cell growth or proliferation, either benign (noncancerous) or malignant (cancerous) including pre-cancerous lesions.

As used herein, the terms "cancer" and "cancerous" refer to or describe the physiological condition in mammals in which a population of cells are characterized by unregulated cell growth. Examples of cancer include, but are not limited to, carcinoma, lymphoma, blastoma, sarcoma, and leukemia. More particular examples of such cancers include liver cancer (e.g., hepatocellular carcinoma (HCC)), colon cancer, colorectal cancer (e.g., colorectal carcinoma), gastrointestinal cancer, pancreatic cancer, lung cancer, breast cancer, and kidney cancer.

"Metastasis" as used herein refers to the process by which a cancer spreads or transfers from the site of origin to other regions of the body with the development of a similar cancerous lesion at the new location. A "metastatic" or "metastasizing" cell is one that loses adhesive contacts with neighboring cells and migrates via the bloodstream or lymph from the primary site of disease to invade neighboring body structures.

The terms "cancer cell", "tumor cell" and grammatical equivalents refer to the total population of cells derived from a tumor or a pre-cancerous lesion including both non-tumorigenic cells, which comprise the bulk of the tumor cell population, and tumorigenic cells (e.g., cancer stem cells).

As used herein, the term "subject" refers to any animal (e.g., a mammal), including, but not limited to, humans, non-human primates, rodents, and the like, which is to be the recipient of a particular treatment. Typically, the terms "subject" and "patient" are used interchangeably herein in reference to a human subject.

As used herein, the term "subject suspected of having cancer" refers to a subject that presents one or more symptoms indicative of a cancer (e.g., a noticeable lump or mass) or is being screened for a cancer (e.g., during a routine physical). A subject suspected of having cancer can also have one or more risk factors. A subject suspected of having cancer has generally not been tested for cancer. However, a "subject suspected of having cancer" encompasses an individual who has received an initial diagnosis but for whom the stage of cancer is not known. The term further includes people who once had cancer (e.g., an individual in remission).

As used herein, the term "subject at risk for cancer" refers to a subject with one or more risk factors for developing a specific cancer. Risk factors include, but are not limited to, gender, age, genetic predisposition, environmental exposure, previous incidents of cancer, pre-existing non-cancer diseases, and lifestyle.

As used herein, the term "subject diagnosed with a cancer" refers to a subject who has been tested and found to have cancerous cells. The cancer can be diagnosed using any suitable method, including but not limited to, biopsy, x-ray, blood test, and the diagnostic methods of the present invention.

As used herein, the terms "biopsy tissue", "patient sample", "tumor sample", and "cancer sample" refer to a sample of cells, tissue or fluid that is removed from a subject for the purpose of determining if the sample contains cancerous tissue, including cancer stem cells or for determining gene expression profile of that cancerous tissue. In some embodiments, biopsy tissue or fluid is obtained because a subject is suspected of having cancer. The biopsy tissue or fluid is then examined for the presence or absence of cancer, cancer stem cells, and/or cancer stem cell gene signature expression.

As used herein, the term "characterizing cancer in a subject" refers to the identification of one or more properties of a cancer sample in a subject, including but not limited to, the presence of benign, pre-cancerous or cancerous tissue, the stage of the cancer, and the subject's prognosis. Cancers can be characterized by the identification of the expression of one or more cancer marker genes, including but not limited to, any cancer markers disclosed herein.

As used herein, the term "gene expression" refers to the process of converting genetic information encoded in a gene into RNA (e.g., mRNA, rRNA, tRNA, or snRNA) through "transcription" of the gene (e.g., via the enzymatic action of an RNA polymerase), and for protein encoding genes, into protein through "translation" of mRNA. Gene expression can be regulated at many stages in the process. "Up-regulation" or "activation" refers to regulation that increases the production of gene expression products (e.g., RNA or protein), while "down-regulation" or "repression" refers to regulation that decrease production. Molecules (e.g., transcription factors) that are involved in up-regulation or down-regulation are often called "activators" and "repressors," respectively.

The terms "high levels", "increased levels", "high expression", "increased expression", "elevated levels" or "up-regulated expression" in regard to gene expression are used herein interchangeably to refer to expression of a gene in a cell or population of cells at levels higher than the expression of that gene in a second cell or population of cells. In certain embodiments, "high levels", "increased levels", "high expression", "increased expression", "elevated levels" or "up-regulated expression" can be determined by detecting the amount of a polynucleotide (mRNA, cDNA, etc.) in tumor cells, for example, by quantitative RT-PCR or microarray analysis; or by detecting the amount of a protein in tumor cells, for example, by ELISA, Western blot, quantitative immunofluorescence.

As used herein, the terms "low levels", "decreased levels", "low expression", "reduced expression" or "decreased expression" in regards to gene expression are used herein interchangeably to refer to expression of a gene in a cell or population of cells, at levels less than the expression of that gene in a second cell or population of cells. "Low levels" of gene expression can be determined by detecting decreased to nearly undetectable amounts of a polynucleotide (mRNA, cDNA, etc.) in tumor cells, for example, by quantitative RT-PCR or microarray analysis. Alternatively "low levels" of gene expression can be determined by detecting decreased to nearly undetectable amounts of a protein in tumor cells, for example, ELISA, Western blot, or quantitative immunofluorescence.

The term "undetectable levels" or "loss of expression" in regards to gene expression as used herein refers to expression of a gene in a cell or population of cells, at levels that cannot be distinguished from background using conventional techniques such that no expression is identified. "Undetectable levels" of gene expression can be determined by the inability to detect levels of a polynucleotide (mRNA, cDNA, etc.) in tumor cells above background by, for example, quantitative RT-PCR or microarray analysis. Alternatively "undetectable levels" of gene expression can be determined by the inability to detect levels of a protein in tumor cells above background by, for example, ELISA, Western blot, or immunofluorescence.

As used herein, if the expression is "below the level of detection" for a given assay, the expression may still be detectable by another assay.

As used herein, the term "nucleic acid molecule" refers to any nucleic acid containing molecule, including but not limited to, DNA or RNA. The term encompasses sequences that include any of the known base analogs of DNA and RNA including, but not limited to, 4-acetylcytosine, 8-hydroxy-N6-methyladenosine, aziridinylcytosine, pseudoisocytosine, 5-(carboxyhydroxyl-methyl) uracil, 5-fluorouracil, 5-bromouracil, 5-carboxymethylaminomethyl-2-thiouracil, 5-carboxymethylaminomethyluracil, dihydrouracil, inosine, N6-isopentenyladenine, 1-methyladenine, 1-methylpseudouracil, 1-methylguanine, 1-methylinosine, 2,2-dimethyl-guanine, 2-methyladenine, 2-methylguanine, 3-methyl-cytosine, 5-methylcytosine, N6-methyladenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyamino-methyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarbonylmethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid, oxybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, N-uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid, pseudouracil, queosine, 2-thiocytosine, and 2,6-diaminopurine.

The term "gene" refers to a nucleic acid (e.g., DNA) sequence that comprises coding sequences necessary for the production of a polypeptide, precursor, or RNA (e.g., rRNA, tRNA). The polypeptide can be encoded by a full-length coding sequence or by any portion of the coding sequence so long as the desired activities or functional properties (e.g., enzymatic activity, ligand binding, signal transduction, immunogenicity, etc.) of the full-length polypeptide or fragment are retained. The term also encompasses the coding region of a structural gene and the sequences located adjacent to the coding region on both the 5' and 3' ends for a distance of about 1 kb or more on either end such that the gene corresponds to the length of the full-length mRNA. Sequences located 5' of the coding region and present on the mRNA are referred to as 5' non-translated sequences. Sequences located 3' or downstream of the coding region and present on the mRNA are referred to as 3' non-translated sequences. The term "gene" encompasses both cDNA and genomic forms of a gene. A genomic form or clone of a gene contains the coding region interrupted with non-coding sequences termed "introns" or "intervening regions" or "intervening sequences." Introns are segments of a gene that are transcribed into nuclear RNA (hnRNA); introns can contain regulatory elements such as enhancers. Introns are removed or "spliced out" from the nuclear or primary transcript; introns therefore are absent in the messenger RNA (mRNA) transcript. The mRNA functions during translation to specify the sequence or order of amino acids in a nascent polypeptide. A cDNA form of a gene is "intron-free" and non-naturally-occurring.

As used herein, the term "heterologous gene" refers to a gene that is not in its natural environment; thus, it is non-naturally-occurring. For example, a heterologous gene includes a gene from one species introduced into another species. A heterologous gene also includes a gene native to an organism that has been altered in some way (e.g., mutated, added in multiple copies, linked to non-native regulatory sequences, etc.). Heterologous genes are distinguished from endogenous genes in that the heterologous gene sequences are typically joined to DNA sequences that are not found naturally associated with the gene sequences in the chromosome or are associated with portions of the chromosome not found in nature (e.g., genes expressed in loci where the gene is not normally expressed).

As used herein, the term "gene expression" refers to the process of converting genetic information encoded in a gene into RNA (e.g., mRNA, rRNA, tRNA, or snRNA) through "transcription" of the gene (e.g., via the enzymatic action of an RNA polymerase), and for protein encoding genes, into protein through "translation" of mRNA. Gene expression can be regulated at many stages in the process. "Up-regulation" or "activation" refers to regulation that increases the production of gene expression products (e.g., RNA or protein), while "down-regulation" or "repression" refers to regulation that decrease production. Molecules (e.g., transcription factors) that are involved in up-regulation or down-regulation are often called "activators" and "repressors," respectively.

In addition to containing introns, genomic forms of a gene can also include sequences located on both the 5' and 3' end of the sequences that are present on the RNA transcript. These sequences are referred to as "flanking" sequences or regions (these flanking sequences are located 5' or 3' to the non-translated sequences present on the mRNA transcript). The 5' flanking region can contain regulatory sequences such as promoters and enhancers that control or influence the transcription of the gene. The 3' flanking region can contain sequences that direct the termination of transcription, post-transcriptional cleavage and polyadenylation.

As used herein, the terms "nucleic acid molecule encoding," "DNA sequence encoding," and "DNA encoding" refer to the order or sequence of deoxyribonucleotides along a strand of deoxyribonucleic acid. The order of these deoxyribonucleotides determines the order of amino acids along the polypeptide (protein) chain. The DNA sequence thus codes for the amino acid sequence.

"Polypeptide," "peptide" and "protein" are used interchangeably and refer to a polymeric compound comprised of covalently linked amino acid residues.

An "isolated polypeptide," "isolated peptide" or "isolated protein" refer to a polypeptide or protein that is substantially free of those compounds that are normally associated therewith in its natural state (e.g., other proteins or polypeptides, nucleic acids, carbohydrates, lipids). "Isolated" is not meant to exclude artificial or synthetic mixtures with other compounds, or the presence of impurities which do not interfere with biological activity, and which can be present, for example, due to incomplete purification, addition of stabilizers, or compounding into a pharmaceutically acceptable preparation.

As used herein, the term "heterologous polypeptide" refers to a polypeptide that is not in its natural environment; thus, it is non-naturally-occurring. For example, a heterologous polypeptide includes a polypeptide from one species introduced into another species. A heterologous polypeptide

also includes a polypeptide native to an organism that has been altered in some way (e.g., mutated, added in multiple copies, linked to non-polypeptide, etc.). Heterologous polypeptide are distinguished from endogenous polypeptide in that the heterologous polypeptide sequences are typically encoded by cDNA sequences that are not found naturally associated with the gene sequences in the chromosome or are associated with portions of the chromosome not found in nature (e.g., genes expressed in loci where the gene is not normally expressed).

A mutation can be made by any technique for mutagenesis known in the art, including but not limited to, in vitro site-directed mutagenesis (Hutchinson et al. *J. Biol. Chem.* 253:6551 (1978); Zoller et al. *DNA* 3:479 (1984); Oliphant et al. *Gene* 44:177 (1986); Hutchinson et al. *Proc. Natl. Acad. Sci. USA* 83:710 (1986)), use of TAB@linkers (Pharmacia), restriction endonuclease digestion/fragment deletion and substitution, PCR-mediated/oligonucleotide-directed mutagenesis, and the like. PCR-based techniques are preferred for site-directed mutagenesis (see Higuchi, 1989, "Using PCR to Engineer DNA", in PCR Technology: Principles and Applications for DNA Amplification, H. Erlich, ed., Stockton Press, Chapter 6, pp. 61-70).

A "variant" of a polypeptide or protein refers to any analogue, fragment, derivative, or mutant which is derived from a polypeptide or protein and which retains at least one biological property of the polypeptide or protein. Different variants of the polypeptide or protein can exist in nature. These variants can be allelic variations characterized by differences in the nucleotide sequences of the structural gene coding for the protein, or can involve differential splicing or post-translational modification. The skilled artisan can produce non-naturally-occurring variants having single or multiple amino acid substitutions, deletions, additions, or replacements. These variants can include, inter alia: (a) variants in which one or more amino acid residues are substituted with conservative or non-conservative amino acids, (b) variants in which one or more amino acids are added to the polypeptide or protein, (c) variants in which one or more of the amino acids includes a substituent group, and (d) variants in which the polypeptide or protein is fused with another polypeptide such as serum albumin. The techniques for obtaining non-naturally-occurring variants, including genetic (suppressions, deletions, mutations, etc.), chemical, and enzymatic techniques, are known to persons having ordinary skill in the art.

The term "percent identity," as known in the art, is a relationship between two or more polypeptide sequences or two or more polynucleotide sequences, as determined by comparing the sequences. In the art, "identity" also means the degree of sequence relatedness between polypeptide or polynucleotide sequences, as the case may be, as determined by the match between strings of such sequences. "Identity" and "similarity" can be readily calculated by known methods, including but not limited to those described in: Computational Molecular Biology (Lesk, A. M., ed.) Oxford University Press, New York (1988); Biocomputing: Informatics and Genome Projects (Smith, D. W., ed.) Academic Press, New York (1993); Computer Analysis of Sequence Data, Part I (Griffin, A. M., and Griffin, H. G., eds.) Humana Press, New Jersey (1994); Sequence Analysis in Molecular Biology (von Heinje, G., ed.) Academic Press (1987); and Sequence Analysis Primer (Gribskov, M. and Devereux, J., eds.) Stockton Press, New York (1991). Preferred methods to determine identity are designed to give the best match between the sequences tested. Methods to determine identity and similarity are codified in publicly available computer programs. Sequence alignments and percent identity calculations can be performed using sequence analysis software such as the Megalign program of the LASERGENE bioinformatics computing suite (DNASTAR Inc., Madison, Wis.). Multiple alignment of the sequences can be performed using the Clustal method of alignment (Higgins et al., CABIOS. 5:151 (1989)) with the default parameters (GAP PENALTY=10, GAP LENGTH PENALTY=10). Default parameters for pairwise alignments using the Clustal method can be selected: KTUPLE 1, GAP PENALTY=3, WINDOW=5 and DIAGONALS SAVED=5.

The term "sequence analysis software" refers to any computer algorithm or software program that is useful for the analysis of nucleotide or amino acid sequences. "Sequence analysis software" can be commercially available or independently developed. Typical sequence analysis software includes, but is not limited to, the GCG suite of programs (Wisconsin Package Version 9.0, Genetics Computer Group (GCG), Madison, Wis.), BLASTP, BLASTN, BLASTX (Altschul et al., J. Mol. Biol. 215:403 (1990)), and DNASTAR (DNASTAR, Inc. 1228 S. Park St. Madison, Wis. 53715 USA). Within the context of this application it will be understood that where sequence analysis software is used for analysis, that the results of the analysis will be based on the "default values" of the program referenced, unless otherwise specified. As used herein "default values" will mean any set of values or parameters that originally load with the software when first initialized.

As used herein, the term "in vitro" refers to an artificial environment and to processes or reactions that occur within an artificial environment. In vitro environments can consist of, but are not limited to, test tubes and cell culture. The term "in vivo" refers to the natural environment (e.g., an animal or a cell) that can be, but are not limited to, processes or reaction that occur within a natural environment.

As used herein, the term "ex vivo" refers to "outside" the body. The terms "ex vivo" and "in vitro" can be used interchangeably herein.

As used herein, the term "sample" is used in its broadest sense. In one sense, it is meant to include a specimen or culture obtained from any source, as well as biological and environmental samples. Biological samples can be obtained from animals (including humans) and encompass fluids, solids, tissues, and gases. Biological samples include blood products, such as plasma, serum and the like. Environmental samples include environmental material such as surface matter, soil, water, crystals and industrial samples. Such examples are not however to be construed as limiting the sample types applicable to the present invention.

In certain embodiments, terms such as "treating" or "treatment" or "to treat" refer to both 1) therapeutic measures that cure, slow down, lessen symptoms of, and/or halt progression of a diagnosed pathologic condition or disorder and 2) prophylactic or preventative measures that prevent or slow the development of a targeted pathologic condition or disorder. Thus, those in need of treatment include those already with the disorder; those prone to have the disorder; those who may have had the disorder and in whom the disorder may recur; and, those in whom the disorder is to be prevented. In certain embodiments, a subject is successfully "treated" if the patient shows one or more of the following: a reduction in the number of or complete absence of cancer cells; a reduction in the tumor size; inhibition of or an absence of cancer cell infiltration into peripheral organs including the spread of cancer into soft tissue and bone; inhibition of or an absence of tumor metastasis; inhibition or an absence of tumor growth; relief of one or more symptoms

associate with the specific cancer; reduced morbidity and/or mortality; improvement in quality of life; a reduction in the number of or complete absence of cancer stem cells; a decrease in the proportion of cancer stem cells in a solid tumor (relative to cells in the tumor that are not cancer stem cells); inhibit the proliferation of cancer stem cells; and a delay in or an absence of relapse.

In certain embodiments, the term "therapeutically effective amount" refers to an amount of a therapeutic agent, e.g., an antibody, polypeptide, polynucleotide, small organic molecule, or other drug effective to "treat" a disease or disorder in a subject. In the case of cancer, the therapeutically effective amount of the therapeutic agent can, in certain embodiments, reduce the number of cancer cells; reduce the proportion of cancer cells in a solid tumor; reduce the tumor size; inhibit or stop cancer cell infiltration into peripheral organs; inhibit and/or stop tumor metastasis; inhibit and stop tumor growth; relieve to some extent one or more of the symptoms associated with the cancer; inhibit the proliferation of cancer cells; or result in a combination of such effects on cancer cells.

As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the vectors or cells presented herein, its use in therapeutic compositions is contemplated. Supplementary active ingredients also can be incorporated into the compositions.

Mesenchymal Stromal Cell (MSC)

Mesenchymal stromal cells (MSCs) (also referred to as fibroblastic colony forming units or mesenchymal stem cells) constitute a heterogeneous cell population, characterized by their adherence to plastic, fibroblast-like morphology, expression of specific markers (CD105+, CD90+, CD73+), lack of hematopoietic markers (CD45, CD34, CD14 or CD11b, CD79α or CD19) and HLA class II and capability to differentiate in vitro into osteoblasts, adipocytes and chondroblasts (Dominici, M., K. Le Blanc, et al. (2006) Cytotherapy 8(4): 315-317). MSCs are most often derived from bone marrow (BM), but can also be isolated from adipose tissue (AT) or from umbilical cord (youngest, most primitive MSCs); from the latter case, MSCs are isolated from the Wharton's jelly (WJ-MSCs), perivascular areas (Mesenchymal cells harvested from umbilical cord perivascular tissue) or umbilical cord blood (CB-MSCs) (Bernardo, M. E., F. Locatelli, et al. (2009) Ann N Y Acad Sci 1176: 101-117). Other rich sources for MSCs are the developing tooth bud of the mandibular third molar and amniotic fluid. It has also been reported that MSCs can be successfully isolated from human peripheral blood (Chong P P et al. (2012) J Orthop Res. 30(4):634-42). The MSCs can be isolated from the whole umbilical cord and in this case can be referred to as "mesenchymal cells derived from umbilical cord." It is noted that as the umbilical cord has different structures, and the isolation of MSCs can also be made or harvested from only a "region" or "structure" such as the perivascular tissue, the Wharton's jelly, or the umbilical cord blood.

MSCs have a great capacity for self-renewal while maintaining their multipotency. A standard test to confirm multipotency is differentiation of the cells into osteoblasts, adipocytes, and chondrocytes as well as myocytes and neurons. Other attractive features of MSCs include that they are readily isolated from bone marrow by their adherence to tissue culture surfaces, they rapidly expanded in culture, they are highly clonogenic in that they efficiently generated single-cell derived colonies, and they are readily seen to differentiate in culture or in vivo into several cellular phenotypes such as osteoblasts, adipocytes, and chondrocytes. These properties are retained as the cells are expanded through 20 or so population doublings, particularly if the cells were plated at low density and passed before they reach confluency (Gregory C A, et al. (2005) Sci STKE 294:pe37). The plasticity of MSCs was also illustrated by experiments in which MSCs were cultured without fetal calf serum (Pochampally et al. (2004) Blood 103:1647-1652) or, even more dramatically, when the MSCs were subjected to environmental stress in culture to generate multi-lineage-differentiating stress-enduring MSCs or Muse cells (Wakao et al. (2011) Proc Nal Acad Sci USA 108:9875-9880). Under such circumstances, the MSCs reverted to a more primitive phenotype and expressed genes characteristic of embryonic genes.

MCSs have been observed to have anti-inflammatory effects. The disease models in which MSCs have produced beneficial effects include diabetes, stroke, spinal cord injury, Parkinsonism, Alzheimer's disease, liver disease, kidney disease, and some cancers. See Prockop, D. J. and J. Y. Oh (2012) J Cell Biochem 113(5): 1460-1469. MSCs have also been shown to contribute to cancer progression, e.g., hematological malignancies (Torsvik A. and Bjerkvig R. (2013) Cancer Treat Rev. 39(2)180-8).

MSCs have the ability to migrate and engraft tumors and it is thought that factors produced by tumor cells and their microenvironments are responsible. MSC motility in vitro has been induced after stimulation with different cytokines (Ries, Egea et al. (2007). Blood 109(9): 4055-4063), growth factors (Ponte, Marais et al. (2007) Stem Cells 25(7): 1737-1745), or chemokines such as CXCL7 (Kalwitz, Endres et al. (2009) Int J Biochem Cell Biol 41(3): 649-658) or SDF-1 (Gao, Priebe et al. (2009) Stem Cells 27(4): 857-865). However, this application is the first report demonstrating the increased MSCs in vivo migration towards HCC with a simple treatment with rAMF. Reports have demonstrated MSC migration towards a number of tumor-released factors (e.g., VEGF, PDGF, TGF-O, MCP-1, IL-8, TNF-α, IL-10, IL-6, SDF-1, and HGF). However, there is a lack of robust data confirming the role of any specific factors in the recruitment of MSCs towards tumors such as HCC.

MSCs show tropism for inflamed, injured or tumorigenic sites and their ability to be cultured and expanded in vitro, their self-renewal properties and low immunogenicity make these cells useful for cell therapy (Prockop, D. J. and J. Y. Oh (2012) J Cell Biochem 113(5): 1460-1469). Although there are some promising results with MSCs genetically modified as a therapeutic option for HCC (Gao, Yao et al. (2010) Oncogene 29(19): 2784-2794; Niess, Bao et al. (2011) Ann Surg 254(5): 767-774; discussion 774-765), these reports left a need to enhance the efficacy of MSCs migration towards tumor (e.g., HCC) microenvironment. The current application includes certain embodiments where MSCs, e.g., MSCs genetically modified to express an anti-tumor gene, are pretreated with rAMF to increase migration toward a tumor microenvironment.

In some embodiments a method for the genetic modification of MSCs is by chemical (e.g. Lipofectamine) or physical (e.g. electroporation) transfection or viral vectors. Afterwards stably transfected cells can be selected, where the transgene cassette has integrated by chance into the MSC genome. In another embodiment, the genetic modification of MSCs is by using non-viral vector systems derived from

transposons. After flanking of an expression cassette with terminal inverted repeats, a construct can be transferred into MSC via transfection. If a transposase is expressed in trans during the transfection, the expression cassette will be stably integrated into the genome of the MSC.

A genetically modified MSC according to some embodiments of the invention can be prepared by transduction of native MSCs with pseudotyped virions, expressing foreign glycoproteins on their surface, which alter the tropism and often the titer of the virion.

A genetically modified MSC according to some embodiments can be engineered to express an oncolytic virus expressing anti-tumor genes.

Autocrine Motility Factor (AMF)

Autocrine motility factor (AMF) is a 55-kDa cytokine secreted by tumors that regulates cell motility (Liotta, L. A., R. Mandler, et al. (1986) Proc Natl Acad Sci USA 83(10): 3302-3306). AMF exhibits sequence identity with glucose-6-phosphate isomerase (GPI), a glycolytic enzyme involved in carbohydrate metabolism (Watanabe, H., K. Takehana, et al. (1996) Cancer Res 56(13): 2960-2963). The stimulation of cell motility is induced by the binding to the autocrine motility factor receptor (AMFR), a 78-kDa seven transmembrane glycoprotein with leucine zipper and RING-H2 motifs (Shimizu, K., M. Tani, et al. (1999) FEBS Lett 456(2): 295-300). AMFR is stably localized in caveolae, and caveolin-1 (Cav-1) has the ability to regulate the endocytic pathway through the stabilization of caveolae expression (Le, P. U., G. Guay, et al. (2002) J Biol Chem 277(5): 3371-3379).

One of the key steps in the transmigration process across the basement membrane is dependent on the proteolytic activity of metalloproteinases. In tumor cells, AMF-induced motility is mediated by upregulation of MMP2 and MMP3 (Torimura, Ueno et al. (2001) Hepatology 34(1): 62-71; Yu, Liao et al. (2004) Biochem Biophys Res Commun 314(1): 76-82). As disclosed herein, AMF was shown to increase the expression of mRNA MMP3 in MSCs. It was previously reported that MSCs exposed to CM derived from HCC cell lines increased their MMP2 activity (Garcia, Bayo et al. (2011) Mol Pharm 8(5): 1538-1548). As disclosed herein, AMF present in the CM is, at least in part, responsible for the increased in MMP2 activity since blockage of AMF decreased MMP2 activity. In addition, stimulation with rAMF increased the invasion capacity of MSCs across collagen and the MMPs inhibitor significantly decreased the invasion capacity of MSCs.

AMF is produced by several tumors, such as lung (Dobashi, Watanabe et al. (2006) J Pathol 210(4):431-440), gastrointestinal, kidney and breast (Baumann, Kappl et al. (1990) Cancer Invest 8(3-4):351-356 as well as hepatocellular carcinomas (HCC) (Ogata, Torimura et al. (1999) Hum Pathol 30(4): 443-450). It is also reported herein that AMF is secreted in the CM from HCC s.c tumors.

AMF is not considered a typical chemotactic factor such as VEGF, PDGF, TGF-β, MCP-1, IL-8, TNF-α, IL-10, IL-6, SDF-1, and HGF. Instead, intracellular AMF has been shown to be involved in glucose metabolism in all types of cells and some reports have described the extracellular form of AMF as inducing tumor migration and endothelial cell migration related to angiogenesis.

AMF-induced migration has been described in tumor cells and its role in metastasis. In vitro studies have demonstrated that exogenous AMF stimulated migration of human cancer melanoma, fibrosarcoma and HCC cells as well as human umbilical vein endothelial cells (HUVECs) (Liotta, Mandler et al. (1986) Proc Natl Acad Sci USA 83(10): 3302-3306; Silletti, Watanabe et al. (1991) Cancer Res 51(13): 3507-3511; Watanabe, Carmi et al. (1991) J Biol Chem 266(20): 13442-13448; Torimura, Ueno et al. (2001) Hepatology 34(1): 62-71). Overexpression of AMF in NIH-3T3 fibroblasts was reported to induce malignant transformation (Tsutsumi, Hogan et al. (2003) Cancer Res 63(1): 242-249). In embodiments of the current application, rAMF treatment does not induce malignant transformation in MSCs or promote increased tumor development or metastasis.

In cancer cells, it has been observed that AMF-induced migration is mediated by its interaction with AMF receptor (AMFR) on cell surface (Silletti, Watanabe et al. (1991) Cancer Res 51(13): 3507-3511). AMFR has been found stably localized to caveolae at the plasma membrane caveolin-1, a caveolar coat protein that has been described as a negative regulator of caveolae-mediated endocytosis of AMFR to the endoplasmic reticulum (Le, Guay et al. (2002) J Biol Chem 277(5): 3371-3379). It is disclosed herein that rAMF treatment of MSCs induced AMFR and caveolin-1 and -2 expressions, supporting their role in the maintenance of the receptor on the cell surface. Moreover, in cancer cells AMF enhances integrin 01 activity leading to activation of mitogen activated protein kinase (MAPK) and Rho pathways (Torimura, Ueno et al. (2001) Hepatology 34(1): 62-71). Small GTPase is largely involved in motility and cell adhesion due to its role in cytoskeleton organization. GTPase activity is regulated by GTPase-activating proteins (GAPs) and GDP dissociation inhibitors (GDIs). In bladder cancer, Rho GDP dissociation inhibitor (GDI) 0 (GDI2) is diminished in cells with higher motility indicating its role as suppressor of migration. However other reports indicated that GDI2 is upregulated in tumors with a more aggressive phenotype (Tapper, Kettunen et al. (2001) Cancer Genet Cytogenet 128(1): 1-6; Yanagawa, Watanabe et al. (2004) Lab Invest 84(4): 513-522). As disclosed herein, rAMF treatment decreased mRNA of GDI-2, supporting its role as inhibitor of migration. In certain embodiments, rAMF is a chemoattractant factor for MSCs, e.g., MSCs comprising a therapeutic agent.

The AMF can be naturally produced or recombinant. In certain embodiments, the AMF is human AMF. In some embodiments, the AMF comprises the polypeptide sequence of SEQ ID NO:1 or a functional fragment thereof. In some embodiments, the AMF comprises a polypeptide having an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or 100% identical to an AMF amino acid sequence that is naturally produced in an animal (e.g., SEQ ID NO:1). In some embodiments, the AMF comprises or consists of a sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or 100% sequence identity to SEQ ID NO:1 or a functional fragment thereof.

Compositions

Certain embodiments are directed to a composition comprising a mesenchymal stromal cell (MSC) stimulated with a recombinant autocrine motility factor (rAMF), wherein the MSC comprises a therapeutic agent and wherein the MSC of the composition has (1) increased migration to a tumor or a tumor cell after rAMF stimulation and/or (2) increased adhesion to an endothelial cell, e.g., a vascular endothelial cell, after rAMF stimulation.

Certain embodiments are directed to a composition comprising a mesenchymal stromal cell (MSC) stimulated with a recombinant autocrine motility factor (rAMF), wherein the MSC comprises a therapeutic agent and wherein the MSC of the composition has increased migration to a tumor or a

tumor-derived cell. In some embodiments, the increased migration is relative to or compared to MSC without rAMF stimulation.

Certain embodiments are directed to a composition comprising a mesenchymal stromal cell (MSC) stimulated with a recombinant autocrine motility factor (AMF), wherein the MSC comprises a therapeutic agent and wherein the MSC of the composition has increased adhesion to an endothelial cell, e.g., a vascular endothelial cell. In some embodiments, the increased adhesion is relative to or compared to MSC without rAMF stimulation.

In some embodiments, the increased migration and/or adhesion is about 1.5-fold, about 2-fold, about 2.5-fold, or about 3-fold greater than migration and/or adhesion of the MSC without rAMF stimulation. In some embodiments, the increase in migration and/or adhesion is at least about 20-60%, 30-60%, 40-60%, 30-50%, or 20-40% greater than migration and/or adhesion of the MSC without rAMF stimulation.

In some embodiments, the MSC of the composition is selected from the group consisting of bone marrow MSC, adipose tissue MSC, umbilical cord MSC, and any combination thereof.

In some embodiments, the tumor is a solid tumor or cancer. In some embodiments, the tumor is a liver cancer, a colon cancer, a pancreatic cancer, a lung cancer, a gastrointestinal cancer, a kidney cancer, a breast cancer, or a combination thereof. In some embodiments, the tumor is a carcinoma, e.g., hepatocellular carcinoma (HCC) or colorectal carcinoma. In some embodiments, the tumor or the tumor cell expresses endogenous AMF.

In some embodiments, the therapeutic agent is a recombinant anti-tumor gene (e.g., an interferon (e.g., interferon α, interferon β), an interleukin (interleukin 1, interleukin 12), a chemokine (e.g., CX3CL1), a suicide gene (e.g., thymidine kinase, IL-12, IFN-gamma, TNF-alpha), or any combination thereof), a cytotoxic drug, an antibody, or an oncolytic virus.

In some embodiments, the therapeutic agent is an oncolytic virus (OV), i.e., a virus that preferentially infects and kills cancer cells (e.g., adenovirus (e.g., H101), Reovirus, measles, herpes simplex (e.g., HSV1716), Newcastle disease virus and vaccinia). See, e.g., Nakashima et al. (2010) Cytokine Growth Factor Rev. 21(2-3):119-26. In some embodiments, the oncolytic virus is engineered to expresses a recombinant anti-tumor gene. In one embodiment, the recombinant oncolytic virus is an oncolytic adenovirus. In some embodiments, the therapeutic agent is an oncolytic virus (see, e.g., Dwyer R M et al. (2010) Stem Cell Res Ther. 1(3):25), e.g., onyx-015 (see, e.g., Khuri F R et al. (2000) Nat Med. 6(8):879-85); Ad-F512(H-N)5/3 (see, e.g., Viale D. L., et al. (2013) J Invest Dermatol doi: 10.1038/jid.2013.191 (e-publication ahead of print)). In some embodiments, the oncolytic virus can be used as a vector for delivery of anti-tumor genes, e.g., an interferon (e.g., interferon α, interferon β), an interleukin (e.g., interleukin 1, interleukin 12), a chemokine (e.g., CX3CL1), or a suicide gene (e.g., encoding enzymes that can metabolize a separately administered non-toxic pro-drug into a potent cytotoxin, which can diffuse to and kill neighboring cells). In some embodiments, the MSC comprises a recombinant AMF receptor, CXCR1, CXCR2, or MCP-1.

Methods of Increasing Migration or Anchorage

Certain embodiments are directed to a method for increasing migration or anchorage of a mesenchymal stromal cell (MSC) to a tumor comprising (a) stimulating the MSC with a recombinant autocrine motility factor (rAMF), and (b) administering the stimulated MSC of (a) to the tumor, wherein the MSC comprises a therapeutic agent.

In some embodiments, the methods of the application include increasing migration or anchorage of MSCs to a tumor, e.g., a solid tumor or cancer. In some embodiments, the tumor is selected from the group consisting of a liver cancer, a colon cancer, a pancreatic cancer, a lung cancer, a gastrointestinal cancer, a kidney cancer, a breast cancer, and any combination thereof. In some embodiments, the tumor is a carcinoma, e.g., hepatocellular carcinoma (HCC) or colorectal carcinoma. In some embodiments, the tumor or the tumor cell expresses endogenous AMF.

In some embodiments, the methods of the application include increasing migration or anchorage of MSCs to a tumor wherein the MSCs comprise a therapeutic agent, e.g., a recombinant anti-tumor gene (e.g., an interferon (e.g., interferon α, interferon β), an interleukin (interleukin 1, interleukin 12), a chemokine (e.g., CX3CL1), a suicide gene (e.g., thymidine kinase, IL-12, IFN-gamma, TNF-alpha), or any combination thereof), a cytotoxic drug, an antibody, or an oncolytic virus.

In some embodiments, the methods of the application include increasing migration or anchorage of MSCs to a tumor wherein the MSCs comprise a therapeutic agent, e.g., an oncolytic virus (OV), i.e., a virus that preferentially infects and kills cancer cells (e.g., adenovirus (e.g., H101), Reovirus, measles, herpes simplex (e.g., HSV1716), Newcastle disease virus and vaccinia). See, e.g., Nakashima et al. (2010) Cytokine Growth Factor Rev. 21(2-3):119-26. In some embodiments, the oncolytic virus is engineered to expresses a recombinant anti-tumor gene. In one embodiment, the recombinant oncolytic virus is an oncolytic adenovirus, e.g., Ad-F512(H-N)5/3 (see, e.g., Lopez, et al. (2012) Mol Ther. 20(12):2222-33). In some embodiments, the oncolytic virus can be used as a vector for delivery of anti-tumor genes, e.g., an interferon (e.g., interferon α, interferon β), an interleukin (e.g., interleukin 1, interleukin 12), a chemokine (e.g., CX3CL1), or a suicide gene (e.g., encoding enzymes that can metabolize a separately administered non-toxic pro-drug into a potent cytotoxin, which can diffuse to and kill neighboring cells). In some embodiments, the MSC comprises a recombinant AMF receptor, CXCR1, CXCR2, or MCP-1.

Methods of Treatment

Certain aspects of the application are related to cell therapies using cells genetically engineered to express a heterologous gene, e.g., an anti-cancer gene. Some embodiments are directed to a method for treating a subject with a tumor comprising administering to the subject a composition of the application.

Some embodiments are directed to a method for treating a subject with a tumor comprising (a) stimulating a mesenchymal stromal cell (MSC) comprising a therapeutic agent with a recombinant autocrine motility factor (rAMF), and (b) administering the stimulated MSC of (a) to the subject.

In some embodiments, stimulating a MSC with a recombinant protein of the application, e.g., rAMF, is accomplished by pretreatment of the MSC prior to administration to a subject. Methods for pretreating the MSC include, e.g., culturing MSCs with the recombinant protein, e.g., rAMF, for about 1-48 hours, about 6-48 hours, about 6-36 hours, about 6-24 hours, about 12-24 hours, about 12-36 hours, about 12-48 hours, about 18-48 hours, about 18-36 hours, or about 18-24 hours prior to administration of the stimulated MSC.

In some embodiments, the subject's tumor is a solid tumor or cancer. In some embodiments, the tumor is selected from

the group consisting of a liver cancer, a colon cancer, a pancreatic cancer, a lung cancer, a gastrointestinal cancer, a kidney cancer, a breast cancer, and any combination thereof. In some embodiments, the tumor is a carcinoma, e.g., hepatocellular carcinoma (HCC) or colorectal carcinoma. In some embodiments, the tumor expresses endogenous AMF. In some embodiments, the tumor is metastatic and/or vascularized.

In some embodiments, the methods of the application treating a tumor wherein the MSCs comprise a therapeutic agent, e.g., a recombinant anti-tumor gene (e.g., an interferon (e.g., interferon α, interferon β), an interleukin (interleukin 1, interleukin 12), a chemokine (e.g., CX3CL1), a suicide gene (e.g., thymidine kinase, IL-12, IFN-gamma, TNF-alpha), or any combination thereof), a cytotoxic drug, an antibody, or an oncolytic virus.

In some embodiments, the therapeutic agent is an oncolytic virus, i.e., a virus that preferentially infects and kills cancer cells (e.g., adenovirus (e.g., H101), Reovirus, measles, herpes simplex (e.g., HSV1716), Newcastle disease virus and vaccinia). See, e.g., Nakashima et al. (2010) Cytokine Growth Factor Rev. 21(2-3):119-26. In some embodiments, the oncolytic virus is engineered to expresses a recombinant anti-tumor gene. In one embodiment, the recombinant oncolytic virus is an oncolytic adenovirus, e.g., Ad-F512(H-N)5/3 (see, e.g., Lopez, et al. (2012) Mol Ther. 20(12):2222-33). In some embodiments, the oncolytic virus can be used as a vector for delivery of anti-tumor genes, e.g., an interferon (e.g., interferon α, interferon β), an interleukin (e.g., interleukin 1, interleukin 12), a chemokine (e.g., CX3CL1), or a suicide gene (e.g., encoding enzymes that can metabolize a separately administered non-toxic pro-drug into a potent cytotoxin, which can diffuse to and kill neighboring cells). In one embodiment, the suicide gene encodes Herpes simplex viral thymidine kinase, and the subject ideally is treated with ganciclovir in a manner permitting the Herpes simplex viral thymidine kinase to render the ganciclovir cytotoxic. Another possibility is the use of cytosine deaminase as a cytotoxic protein, which converts 5-fluorocytosine to the toxic compound 5-fluorouracil.

In some embodiments, the method for treating a subject with a tumor comprises introducing into the subject's bloodstream a therapeutically effective amount of a rAMF stimulated MSC or composition of the application. In some embodiments, the administration to the subject is systemic (e.g., parenteral) or local, e.g., to an intra-hepatic artery.

In some embodiments, the therapeutically effective number of MSCs includes, without limitation, the following amounts and ranges of amounts: (i) from about 1×10^5 to about 1×10^9 cells/kg body weight; (ii) from about 1×10^6 to about 1×10^8 cells/kg body weight; (iii) from about 5×10^6 to about 2×10^7 cells/kg body weight; (iv) from about 5×10^6 to about 1×10^7 cells/kg body weight; (v) from about 1×10^7 to about 2×10^7 cells/kg body weight; (vi) from about 7×10^6 to about 9×10 cells/kg body weight; (vii) about 1×10 cells/kg body weight; (viii) about 1×10^6 cells/kg body weight; (ix) about 5×10^6 cells/kg body weight; (x) about 1×10^7 cells/kg body weight; (xi) about 6×10^6 cells/kg body weight; (xii) about 7×10^6 cells/kg body weight; (xiii) about 8×10 cells/kg body weight; and (ix) about 9×10^6 cells/kg body weight. Human body weights envisioned include, without limitation, about 50 kg, about 60 kg; about 70 kg; about 80 kg, about 90 kg; and about 100 kg. Therapeutically effective amounts can be based on pre-clinical animal experiments and standard protocols from the transplantation of MSCs.

The practice of the present invention will employ, unless otherwise indicated, conventional techniques of cell biology, cell culture, molecular biology, transgenic biology, microbiology, recombinant DNA, and immunology, which are within the skill of the art. Such techniques are explained fully in the literature. See, for example, Sambrook et al., ed. (1989) Molecular Cloning A Laboratory Manual (2nd ed.; Cold Spring Harbor Laboratory Press); Sambrook et al., ed. (1992) Molecular Cloning: A Laboratory Manual, (Cold Springs Harbor Laboratory, NY); D. N. Glover ed., (1985) DNA Cloning, Volumes I and II; Gait, ed. (1984) Oligonucleotide Synthesis; Mullis et al. U.S. Pat. No. 4,683,195; Hames and Higgins, eds. (1984) Nucleic Acid Hybridization; Hames and Higgins, eds. (1984) Transcription And Translation; Freshney (1987) Culture Of Animal Cells (Alan. Liss, Inc.); Immobilized Cells And Enzymes (IRL Press) (1986); Perbal (1984) A Practical Guide To Molecular Cloning; the treatise, Methods In Enzymology (Academic Press, Inc., N.Y.); Miller and Calos eds. (1987) Gene Transfer Vectors For Mammalian Cells, (Cold Spring Harbor Laboratory); Wu et al., eds., Methods In Enzymology, Vols. 154 and 155; Mayer and Walker, eds. (1987) Immunochemical Methods In Cell And Molecular Biology (Academic Press, London); Weir and Blackwell, eds., (1986) Handbook Of Experimental Immunology, Volumes I-IV; Manipulating the Mouse Embryo, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., (1986); and in Ausubel et al. (1989) Current Protocols in Molecular Biology (John Wiley and Sons, Baltimore, Md.).

The following examples are offered by way of illustration and not by way of limitation.

EXAMPLES

Example 1

Materials and Methods

Cell Lines

Human HCC cell line HuH7 were kindly provided by Prof. Jesus Prieto (CIMA, University of Navarra, Pamplona, Spain). LX-2 cell line (human HSCs generated by spontaneous immortalization in low serum conditions) was kindly provided by Dr. Scott Friedman (Division of Liver Diseases, Mount Sinai School of Medicine, New York, N.Y., USA). Human microvascular endothelial cells (HMEC-1) were provided by CDC (Centers for Disease Control, Atlanta, Ga., USA). Cell lines were cultured in complete DMEM (2 μmol/L glutamine, 100 U/mL penicillin, 100 mg/mL streptomycin and 10% heat-inactivated fetal bovine serum (FBS)). Primary culture of HCC cells (HC-PT-5) was previously generated in our laboratory and cultured the eight passage in 70% DMEM/30% F12 (Invitrogen/Life Technologies) culture medium supplemented with 2 μmol/L glutamine, 100 units/mL penicillin, 100 mg/mL streptomycin and 10% FBS.

Isolation of MSCs, AT-MSCs and Mesenchymal Cells Harvested from Umbilical Cord Perivascular Tissue

Cells were obtained from allogeneic bone marrow transplantation of healthy donors after informed consent (Hospital Naval Pedro Mallo, Buenos Aires, Argentina). Mononuclear cells were plated in complete DMEM low glucose/20% FBS (Intemegocios S.A., Argentina). After 2 h incubation, non-adherent cells were removed and adherent hMSCs were cultured and used for different experiments between passages 4 to 6. For AT-MSCs generation, cells were isolated from discarded fat from esthetical liposuctions

after informed consent as described previously Zuk et al. (Zuk, Zhu et al. (2001). Tissue Eng 7(2):211-228). Briefly, discarded lipoaspirates were washed extensively with sterile phosphate-buffered saline. Washed aspirates were treated with 0.075% type collagenase (Sigma-Aldrich) in PBS for 30 min at 37° C. with agitation. The cells were centrifugated and cellular pellet was plated in complete DMEM low glucose/20% FBS (Intemegocios S.A., Argentina) and used for different experiments between passages 4 to 6.

Mesenchymal cells harvested from umbilical cord perivascular tissue were isolated from discarded umbilical cord obtained from healthy donors from the Service of Gynaecology and Obstetrics after informed consent in our institution adapted from the protocol previously described in Sarugaser, Lickorish et al. (2005). Stem Cells 23(2):220-229). Umbilical cords were dissected and vessels with its surrounding Warthon's Jelly were pulled out. Then the perivascular Wharton's Jelly were removed from the vessels and mechanically disrupted. Minced fragments were plated in complete DMEM low glucose/20% FBS (Intemegocios S.A., Argentina). After 7 days incubation, non-adherent cells and minced fragments were removed and adherents Mesenchymal cells harvested from umbilical cord perivascular tissue were cultured and used for different experiments between passages 4 to 6.

MSCs were characterized according to the guidelines from International society for cellular therapy (ISCT).

Conditioned Medium

To obtain tumor conditioned medium (TCM), HuH7 or HC-PT-5 subcutaneous tumors (s.c.) were dissected and minced into pieces smaller than 1 mm^3 and transferred into a 24 wells tissue culture plate (6 fragments/well) with 500 μl of DMEM supplemented with 2 μmol/l glutamine, 100 units/ml penicillin, and 100 mg/ml streptomycin. Cell conditioned medium (CCM) was obtained from HCC cell lines cultured as described above to 90% confluence and then were washed with PBS and cultured with DMEM without FBS. In both cases, 18 hours later conditioned medium was harvested and stored at −80° C. until use.

Western Blot

BM-MSCs or AMF stimulated BM-MSC were lysed with 150 mmol/L NaCl, 20 mmol/L Tris-HCl, pH 7.4, 0.1% SDS, 1.0% Nonidet P-40, 0.5% Na-deoxycholate, 0.2 mmol/L phenylmethylsulfonyl fluoride, and protease inhibitor cocktail. Lysates were centrifuged at 12,000 g for 20 min and the supernatants were used as total cell lysates. CCM and TCM were concentrated 100-fold using Vivaspin 6 centrifugal concentrator (Sartorius-Stedim Biotech). The protein concentration was determined by Bradford protein assay (Bio-Rad). Protein was separated by SDS-PAGE and transferred onto nitrocellulose membrane (Hybond-ECL, Amersham Biosciences). Blots were blocked and incubated with anti-AMF (1:700) polyclonal antibody (sc-33777, Santa Cruz Biotechnology), anti-AMFR (1:1000) polyclonal antibody (AP2162a, ABGENT), anti-JNK (1:1000) polyclonal antibody (9252, Cell Signaling), anti-phospho-JNK (1:1000) polyclonal antibody (9251, Cell Signaling), anti-c-Fos (1:1000) monoclonal antibody (2250, Cell Signaling), anti-phospho-c-Fos (1:1000) monoclonal antibody (5348, Cell Signaling), anti-phospho-CREB (1:1000) monoclonal antibody (9198, Cell Signaling) or anti-Actin (1:700) polyclonal antibody (sc-1615, Santa Cruz Biotechnology) at 4° C. overnight. Finally, blots were then incubated with the corresponding HRP-conjugated IgG at room temperature for 1 hour. The reactions were visualized using the enhanced chemiluminescence (ECL) reagent (Sigma). Staining with colloidal Coomassie was performed as loading control for conditioned medium as was reported previously (Welinder, Ekblad. (2011) J Proteome Res 10(3):1416-1419). Density of each band was quantified with Scion Image software (Scion Corporation, Frederick, Md.).

In Vitro Migration, Invasion, and Wound-Healing Assays

In vitro migration was performed using a 48-Transwell microchemotaxis Boyden Chamber unit (Neuroprobe, Inc.). In brief, MSCs (1.2×10^3 cells/well) were placed in the upper chamber and DMEM, TCM or recombinant human AMF (rAMF) where placed in the lower chamber of the Transwell unit. Both chambers were separated by 8 μm pore polycarbonate filters (Nucleopore membrane, Neuroprobe). For blocking experiments, TCM were pre-incubated for 60 min with anti-AMF polyclonal antibody (sc-33777, Santa Cruz Biotechnology) or isotype control IgG. For AMF pre-treatment BM-MSCs were incubated overnight (O.N.) with 1 μg/ml of rAMF in DMEM without FBS or DMEM without FBS as control.

For the invasion assay the polycarbonate filters were previously incubated with 10 mg/ml type IV collagen (Sigma-Aldrich) for 18 h at 4° C.; for MMP inhibition, BM-MSCs were preincubated with 1,10 phenantroline (0.5 or 1 mM) (Sigma-Aldrich). MSCs viability was not affected by 1,10 phenantroline (not shown). All the systems were incubated for 4 h at 37° C. in a 5% CO_2 humidified atmosphere. After that, the membrane was carefully removed and cells on the upper side of the membrane were scraped off with a blade. Cells attached to the lower side of the membrane were fixed in 2% formaldehyde, and stained with 40,6-diamidino-2-phenylindole dihydrochloride (DAPI, Sigma-Aldrich). Cells were counted using fluorescent-field microscopy and a 10× objective lens: the images captured in three representative visual fields were analyzed using CellProfiler world wide web A software (world wide web.cellprofile.com), and the mean number of cells/field+ SEM was calculated.

For the wound-healing assay, Fast-DiO-stained MSCs were seeded at 2.5×104 cell/cm^2 in DMEM with 10% FBS for 24 hours. Then, cells were preincubated overnight with 1 μg/ml rAMF or DMEM without FBS. The monolayers were then scratched by a 200 ml-tip, washed with PBS and incubated for 24 hours more in DMEM without FBS. Cells within the scratched area were counted under a fluorescent-field microscope at 40× and the number of cells/field were determined. Additionally, adherent cells were counted at the end of the experiment confirming the same number of cells in all the conditions.

Gelatin Zymography Assay

To evaluate whether AMF induced gelatinolytic activity in MSCs, 5×10^4 cells were seeded in 24-well plates for 18 h. Cells were treated with 1 μg/ml of rAMF, TCM or serum-free DMEM as untreated control for 2 h; then, MSCs were washed with PBS and cultured in DMEM for 6 h before supernatants were collected. For blocking experiments, TCM were pre-incubated for 60 min with anti-AMF polyclonal antibody (sc-33777, Santa Cruz Biotechnology) or isotype control IgG. MMP2 activity was determined by zymography. Briefly, 20 μL of MSC supernatant was run on a 10% SDS-PAGE containing 0.1% gelatin (Sigma-Aldrich). The gel was stained with Coomassie Brilliant Blue R-250 for 30 min at room temperature. Gelatinase activity was visualized by negative staining; el images were obtained with a digital camera (Canon EOS 5D), and were subjected to densitometry analysis using Scion Image software (Scion Corporation, Frederick, Md.). Relative MMP2 activity was obtained by normalizing values to untreated samples (DMEM).

Cell Adhesion Assays

For analyses of MSC adhesion to endothelial cells, 2×10^5 HMEC-1 were seeded in 96-well microplates and cultured for 1 day prior the assay. Coated wells were incubated for 5 minutes with 0.1 ml of 5×10^4 cells/ml of Fast-DiO labeled MSCs O.N. pretreated or not with 1 μg/ml rAMF. The cell suspension was discarded and the cells were fixed with 2% paraformaldehyde. Cells were counted using fluorescent-field microscopy and a 20× objective lens: the images captured in ten representative visual fields were analyzed using CellProfiler software (cellprofiler.com) and normalizing to untreated control.

Reverse Transcription-Polymerase Chain Reaction (RT-PCR)

Total mRNA of BM-MSCs O.N. pretreated or not with 1 μg/ml rAMF was extracted using Trizol Reagent (Sigma-Aldrich Co., St. Louis, Mo.). For quantification of MMP3 mRNA level, MSCs were 24 h starved before rAMF pretreatment. Total mRNA (4 μg) was reverse transcribed with 200 U of SuperScript II Reverse Transcriptase (Invitrogen, Carlsbad, Calif.) using 500 ng of Oligo (dT) primers. cDNAs were subjected to real-time polymerase chain reaction (qPCR) (Stratagene Mx3005p, Stratagene, La Jolla, Calif., USA). For qRT-PCR, the mRNA levels of metalloproteinase 3 MMP3, AMF receptor (AMFR), GDP dissociation inhibitor 2 (GDI-2), caveolin-1 (CAV-1) and caveolin-2 (CAV-2) were quantified by SYBR® Green (Invitrogen), using the following primer pairs:

(SEQ ID NO: 2)
MMP3 5'-ACGCCAGCCAACTGTGATCCT-3' (forward),

(SEQ ID NO: 3)
5'-ATATGCGGCATCCACGCCTGAA-3' (reverse);

(SEQ ID NO: 4)
AMFR 5'-ACAAGATGTGGGCCTTGCAAGA -3 (forward),

(SEQ ID NO: 5)
5'-AAAACGCAGTGCTCCCAGGATA-3' (reverse);

(SEQ ID NO: 6)
GDI-2 5'-GACCAGCTTTGGAGCTCTTG-3' (forward),

(SEQ ID NO: 7)
5'-TGCGGGAAATAAAGATCTGG-3' (reverse);

(SEQ ID NO: 8)
CAV-1 5'-AATCCAAGCATCCCTTTGCCCA-3' (forward),

(SEQ ID NO: 9)
5'-ACCAGGCAGCTTTCTGTACGA-3' (reverse);

(SEQ ID NO: 10)
CAV-2 5'-GAGAGACAGGGGAGTTGTCAACTT-3' (forward),

(SEQ ID NO: 11)
5'-GCCCGGCCCAGAAATAATGAGAT-3' (reverse);

(SEQ ID NO: 14)
CXCR1 5'-TTTTCCGCCAGGCTTACCAT-3' (forward),
and

(SEQ ID NO: 15)
5'-AACACCATCCGCCATTTTGC-3' (reverse);

(SEQ ID NO: 16)
CXCR2 5'-TAAGTGGAGCCCCGTGGGG-3' (forward),
and

(SEQ ID NO: 17)
5'-TGGGCTCAGGGGCAGGATG-3' (reverse);

-continued

(SEQ ID NO: 18)
CCR2 5'-CGAGAGCGGTGAAGAAGTCA-3' (forward),
and

(SEQ ID NO: 19)
5'-AGCATGTTGCCCACAAAACC-3' (reverse);

(SEQ ID NO: 20)
IL-6R 5'-GCACTTGCTGGTGGATGTTC-3 (forward),
and

(SEQ ID NO: 21)
5'-AGCCTTTGTCGTCAGGGATG-3' (reverse);

(SEQ ID NO: 22)
IL-65T 5'-CCCACCTCATGCACTGTTGA-3' (forward),
and

(SEQ ID NO: 23)
5'-TTATGTGGCGGATTCGGCTT-3' (reverse);
and

(SEQ ID NO: 24)
IGFBP3 5'-ACTGTGGCCATGACTGAG-3' (forward),
and

(SEQ ID NO: 25)
5'-AGAGTCTCCCTGAGCCTGA-3' (reverse).

All PCR amplifications were carried out using a cycle of 95° C. for 10 min and 45 cycles under the following parameters: 95° C. for 30 sec, 58° C. for 30 sec, 72° C. for 1 min. At the end of the PCR reaction, the temperature was increased from 60° C. to 95° C. at a rate of 2° C./min, and the fluorescence was measured every 15 sec to construct the melting curve. Values were normalized to levels of glyceraldehyde-3-phosphate dehydrogenase (GAPDH; used as housekeeping) transcript (forward 5'-CATCTCTGCCCCCTCTGCTG-3' (SEQ ID NO: 12); reverse 5'-GCCTGCTTCACCACCTTCTTG-3' (SEQ ID NO: 13)). Data were processed by the AACt method (Livak K J, Schmittgen T D. (2001) Methods 25(4):402-408).

The relative amount of the PCR product amplified from untreated cells was set as 1. A non-template control (NTC) was run in every assay, and all determinations were performed in triplicate in three separated experiments.

Proliferation Assays

HCC cells were seeded in 96-well culture tissue plates at 3×10^4 cells/cm^2 density for 1 day prior to the assay. Then cells were cultured with CM of BM-MSCs pre-treated with 1 μg/ml of rAMF for 48 h. DMEM and CM of untreated BM-MSCs were used as control. Cell proliferation was evaluated by [3H]-thymidine incorporation assay. Each sample was assayed in sextuplicate and normalized to DMEM control.

Three-Dimensional Spheroids

Ninety-six-well tissue culture plates were coated with 2% agarose in PBS. A total of 3×10^3 HuH7 cells, 1×10^3 LX-2, 1×10^3 HMEC-1 with or without 1×10^3 BM-MSC per spheroid were mixed in complete DMEM to obtain a single multicellular spheroid per well. Seventy-five microliters of supernatant was carefully removed from each well every 2 days and replaced with fresh medium or CM from BM-MSC. Viability above 75% was confirmed by Trypan blue exclusion test in all experiments. Spheroid size was evaluated using inverted microscopy and a 4× objective lens: the images were captured and diameters determined using ImageJ software (National Institute of Health, NIH), finally spheroid volume was determined was calculated by the formula $\pi/6\times$larger diameter$\times$(smaller diameter)^2 and expressed as arbitrary unity.

Mice and In Vivo Experiments

Six- to eight-week-old male nude BALB/c mice were purchased from CNEA (Comisión Nacional de Energia Atómica, Ezeiza, Buenos Aires, Argentina). The animals were maintained at our Animal Resources Facilities (School of Biomedical Sciences, Austral University) in accordance with the experimental ethical committee and the NIH guidelines on the ethical use of animals. Subcutaneous model: HuH7 cells (2×10^6) or HC-PT-5 cells (5×10^6) were inoculated subcutaneously (s.c.) into the right flank of nude mice. To evaluate the effect of BM-MSCs pre-treated with recombinant human AMF (rAMF) on tumor development, s.c. HuH7 tumors were established and after 10 days BM-MSCs or BM-MSCs pre-treated with rAMF were intravenously (i.v.) injected. Tumor growth was assessed by calliper measurement, and tumor volume (mm^3) was calculated by the formula $\pi/6\times$ larger diameter$\times$(smaller diameter)^2. For in vivo migration studies, BM-MSCs or BM-MSCs pre-treated with rAMF were prestained with CMDiI for histological analysis and DiR (Molecular Probes, Invitrogen) for fluorescence imaging (FI) and were i.v. injected (5×10 cells/mice) 10 days after tumor inoculation. FI was performed using the Xenogen In Vivo Imaging System (IVIS; Caliper Life Sciences, Hopkinton, Mass., USA). Mice injected with CMDiI-DiR-labeled MSCs were analyzed 1 h after MSC injection and every day until the experimental end point. Images represent the radiant efficiency and were analyzed with IVIS Living Image (Caliper Life Sciences) software. Regions of interest (ROI) were automatically drawn around the isolated organs to assess the fluorescence signal emitted. Results were expressed as average radiant efficiency in units of photons/second within the region of interest [p/s/cm^2/sr]/[$\mu W/cm^2$] or as total radiant efficiency in units of photons/second within the region of interest [p/s]/$\mu W/cm^2$.

Detection of BM-MSC by Fluorescence

To detect CMDiI+ cells within tumors, frozen sections were mounted in mounting media with DAPI (Vector Laboratories, Inc.) and observed under a fluorescence microscope using a 20$\times$ objective lens.

Statistical Analyses

Unpaired Student's t test, one-way analysis of variance following by post tests or Kruskal-Wallis and Dunn's post-tests (GraphPad Prism Software) were used for statistical analyses. Differences with p values lower than 0.05 were considered as statistically significant.

Example 2

Identification of Secreted Factors from HCC Microenvironment

Factors secreted from hepatocellular carcinoma (HCC) microenvironment were identified. Tumor conditioned media (TCM) were obtained from fresh HCC samples or tumors generated from primary cultured human HCC cells (HC-PT-5) or the HuH7 cell line in BALB/c nude mice.

In vitro migratory capacity of MSCs to different TCM samples was analyzed using a 48-Transwell microchemotaxis Boyden Chamber unit (Neuroprobe, Inc.).

Factors present in the different TCM were identified using two Human Cytokine and Chemokine Antibody Arrays (RayBiotech). The factors identified are shown in Tables 1 and 2.

Changes in the gene expression patterns in MSCs exposed to TCM derived from HCC samples were also analyzed. MSCs were exposed overnight to TCM or DMEM (as control) and studied using a microarray gene expression analysis with the aim to identify genes that were differentially expressed in MSCs exposed or not to TCM. Table 3 shows 445 genes differentially expressed in MSC exposed to TCM from sample 1 in comparison with non-exposed cells. Table 4 shows 511 genes differentially expressed in MSC exposed to TCM from sample 2 in comparison with non-exposed cells. Table 5 shows 521 genes differentially expressed in MSC exposed to TCM from sample 4 in comparison with non-exposed cells. Table 6 shows 511 genes differentially expressed in MSC exposed to TCM from sample 5 in comparison with non-exposed cells.

Expression of receptors recognized by soluble factors were analyzed. Receptors with positive signal in at least two of the three replicates of microarray are listed in Table 7.

Real-time PCR (qRT-PCR) was used to analyze the expression of selected genes related to migration in MSCs exposed to TCM. FIG. **1**A shows the relative mRNA expression of up-regulated genes CTGF, CYR61, GJA1, SPARC, and AMFR. Autocrine Motility Factor Receptor (AMFR) was up-regulated in MSCs exposed to all CM derived from HCC samples. FIG. **1** shows relative mRNA expression of down-regulated genes HSPA1A, HSP1B, and IGFBP3.

Example 3

Recombinant AMF Exerts a Specific Chemoatractant Activity on MSCs from Different Sources

The tumor conditioned media (TCM) from ex vivo subcutaneous (s.c.) tumors derived from HuH7 cell line or HC-PT-5 HCC primary culture and conditioned media from cell culture monolayers (CCM) were subjected to western blot analysis according to the method described in Example 1. A 55 kDa soluble AMF was detected in CCM and TCM (FIG. **2**A).

The ability of recombinant human AMF (rAMF) to induce MSCs chemotaxis in vitro was analyzed. MSCs from different sources were evaluated by in vitro migration assay with modified Boyden chambers as described in Example 1. Human MSCs derived from bone marrow (BM-MSCs), perivascular umbilical cord region (Mesenchymal cells harvested from umbilical cord perivascular tissue), or adipose tissue (AT-MSCs) were used in a modified Boyden chamber assay.

The MSCs from the different sources migrated in a dose-dependent manner towards recombinant AMF (FIG. **2**B-D). The most significant migration degree was shown in the dose ranging between 0.5 μg/mL and 1 μg/mL ($p<0.01$) of rAMF for both BM-MSC and Mesenchymal cells harvested from umbilical cord perivascular tissue (FIG. **2**B-C), while AT-MSCs migrated better at 0.75 μg/mL of rAMF (FIG. **2**D). Interestingly, higher rAMF concentration (5 μg/mL or 10 μg/mL) were not capable of inducing migration neither in BM-MSCs nor in Mesenchymal cells harvested from umbilical cord perivascular tissue and AT-MSCs.

Next, TCM were pretreated with polyclonal antibody against AMF (anti-AMF) to examine whether HCC tumor-secreted AMF was involved in MSC migration as described in the methods of Example 1. As shown in FIG. **2**E-G, antibody blocking of AMF present in the TCM from either HuH7 or HC-PT-5 reduced their capability to induce MSC migration in a dose dependent manner. At 1 μg/mL of anti-AMF, BM-MSCs showed a 40% reduction of migration in response to TCM derived from both HCC tumors. A similar effect was observed in Mesenchymal cells harvested from umbilical cord perivascular tissue with a reduction of

30% and 40% in the response to TCM from HuH7 and HC-PT-5, respectively. Finally, the reduction in AT-MSC migration potential was 30% and 20% towards TCM from HuH7 and HC-PT-5, respectively. These results show that AMF exerted a potent chemotactic role in HCC tumor cells.

These results show that AMF was secreted in the culture monolayers from HCC s.c tumors. Moreover, the results show for the first time that AMF produced by HCC is a chemoattractant factor for MSCs and induces migration of MSCs. The migration was shown using MSCs from different sources (i.e., bone marrow (BM), perivascular cells from umbilical cord (Mesenchymal cells harvested from umbilical cord perivascular tissue) and adipose tissue (AT-MSCs)) and the MSCs from all of he tested sources exhibited migration towards AMF in a dose-dependent manner. 1 μg/ml of AMF was sufficient to induce MSCs migration.

Example 4

AMF Stimulates Matrix Metalloproteinase (MMPs) Activity on MSCs

One of the key steps in the transmigration process across the basement membrane is dependent on the proteolytic activity of metalloproteinases. The effect of rAMF on the MSC metalloproteinase activity needed for cell migration was characterized.

MMP3 mRNA level in MSCs was evaluated by qRT-PCR as described in Example 1. MMP3 transcripts showed a 2.4-fold increase in BM-MSCs and Mesenchymal cells harvested from umbilical cord perivascular tissue, and 1.4-fold in AT-MSCs exposed to rAMF compared to unexposed cells (FIG. **3**A).

BM-MSCs stimulated with HCC CCM had increased MMP2 activity. As previously reported (Garcia, Bayo et al. (2011). Mol Pharm 8(5):1538-1548), gelatinolytic activity corresponding to MMP2 was detected in supernatants from BM-MSCs and also from Mesenchymal cells harvested from umbilical cord perivascular tissue and AT-MSCs. In the present example, MMP2 activity was measured by zymography (as described in Example 1) in MSCs culture supernatant pre-stimulated with 1 μg/mL of rAMF or from un-stimulated cells as control to determine whether the induction of MMP2 was dependent on the presence of AMF in the TCM. MMP2 activity was significantly enhanced when different sources MSCs were stimulated with rAMF (FIG. **3**B).

MMP2 activity was also measured in MSC culture supernatant stimulated with TCM derived from HuH7 previously blocked with polyclonal Ab anti-AMF. As a result, the increased MMP2 activity previously observed was completely abolished when MSCs were treated with AMF blocked-TCM showing a similar level of MMP2 activity than untreated cells (FIG. **3**C).

Stimulation with rAMF increased the invasion capacity of MSCs across collagen and the MMPs inhibitor significantly decreased the invasion capacity of MSCs. (FIG. **3**D).

These results show that MMP3 expression and MMP2 activity was induced in MSCs by rAMF. In particular, rAMF increased the expression of mRNA MMP3 in MSCs. The results also show that AMF present in the TCM was, at least in part, responsible for the increased in MMP2 activity, which supports a critical role for AMF in MSC migration and invasion since blockage of AMF decreased MMP2 activity and inhibition of MMP2 decreased invasion in vitro.

Example 5

AMF Enhances BM-MSCs Migration Towards HCC by Stimulating Endothelial Cell Adhesion and Modulating Critical Related Genes

Specific MSC migration to HCC is critical for their use as cell carriers of therapeutic genes. MSCs were pretreated with rAMF to determine the effect of MSC migration towards the HCC TCMs. In vitro migration assay was used to measure migration of MSCs as described in Example 1.

As shown in FIG. **4**A, rAMF pretreatment induced a 40% increase in BM-MSCs migration to conditioned medium from ex vivo s.c. tumors (TCM) derived from HuH7 or HC-PT-5 cell lines. These results show that rAMF pretreatment influenced migration of MSCs towards TCM.

By wound-healing assay, it was observed that overnight rAMF pretreatment did not modify MSC general motility (FIG. **4**B) indicating that rAMF pretreatment increases specific chemotaxis towards HCC.

Adhesion to endothelial cells is considered a crucial event for the efficient arrest of MSCs within tumor vasculature for subsequent transmigration. The effect of rAMF on cell adhesion was tested by pretreating MSCs with rAMF and measuring cell adhesion as described in Example 1. Pretreatment with rAMF resulted in a 2-fold enhancement in BM-MSCs adhesion to human endothelial cells HMEC-1 (FIG. **4**C).

Genes related to the AMF-AMFR pathway were also studied. As shown in FIG. **4**D, a 1.8-fold induction of AMF receptor mRNA was observed when BM-MSCs were stimulated with rAMF. Additionally, mRNA levels of caveolin-1 (CAV-1) and caveolin-2 (CAV-2) were increased in 2.4-fold and 2.3-fold respectively, while Rho GDP dissociation inhibitor (GDI) 0 (GDI-2) expression was reduced 10% after rAMF treatment in BM-MSCs. Moreover, rAMF treatment induced the expression of AMFR, and the proteins involved in AMF-AMFR signaling pathways such as JNK, p-JNK, c-Fos, p-c-Fos and p-CREB (FIG. **4**E).

These results demonstrated that pretreatment with rAMF significantly increased MSC migration towards HCC in vitro and increased MSC adhesion to endothelial cells. Furthermore, these results show that rAMF treatment induced AMFR and caveolin-1 and -2 (genes having a possible role in maintenance of the receptor on the cell surface) expression and decreased GDI-2 (a gene having a possible role as inhibitor of migration) mRNA expression. AMFR and activation of mitogen activated protein kinase (MAPK) pathway was observed after rAMF treatment.

Example 6

Recombinant AMF Increases the In Vivo Homing of MSCs into HCC

Enhancement of MSC migration towards HCC by rAMF stimulation was studied in vivo. Noninvasive fluorescence imaging (FI) was used to measure migration of MSCs as described in Example 1. Human MSCs derived from bone marrow (BM-MSCs) pre-stimulated with rAMF (Ipg/mL) or control BM-MSCs (no stimulation) were stained with cell trackers DiR and CM-DiI prior to intravenous injection in mice carrying s.c. HuH7 tumor nodules as described in Example 1. Three days later, mice were sacrificed and the fluorescence signal in the isolated tumors was analyzed. The total fluorescent intensity in both groups of animals were similar, indicating no differences in the quantity of injected

BM-MSCs (FIG. **5**A). Tumors from animals injected with rAMF-pretreated BM-MSCs showed a stronger DiR signal in comparison with control mice (FIG. **5**B-C). Mice that received BM-MSC pretreated with rAMF did not show increased signal in liver, lung or spleen (FIG. **5**D-F), indicating a specific increased recruitment of BM-MSCs in tumor microenvironment. The presence of BM-MSCs in the isolated tumors was confirmed by cell visualization under fluorescence microscopy (FIG. **5**G). rAMF increased in vivo migration to HCC tumors. These results show that stimulation of MSCs with rAMF increased in vivo migration of MSCs towards experimental HCC tumors in comparison with non-stimulated MSCs.

In vitro studies indicated that HuH7 HCC cells exposed to CCM from MSC pre-treated with rAMF did not enhance cell proliferation compared to unexposed cells or to HuH7 cells exposed to CCM from untreated MSCs (FIG. **6**A). Moreover, pretreatment of MSCs with AMF did not affect the in vitro growth of multicellular spheroids composed of HuH7 HCC cells, hepatic stellate cells LX-2 and HMEC-1 endothelial cells (FIG. **6**B). Finally, AMF-prestimulated MSCs did not enhance tumor growth compared to control tumor-bearing mice (saline) or to the group of mice administered with unstimulated MSCs (FIG. **6**C). These studies indicated, as a whole, that AMF promoted MSC homing to the HCC niche without affecting tumor growth.

Pretreatment with rAMF was shown to significantly increase (by 30%, p0,01) MSCs migration towards HCC in vivo. This is the first report demonstrating the increased in vivo migration of MSCs towards HCC with pretreatment of MSCs with rAMF.

Example 7

HUCPVCs Presented Higher Migration and Adhesion than BM-MSCs

In vitro migration assays were performed as described in Example 1. Specifically, in vitro migration of bone marrow-derived mesenchymal stem cells (BM-MSCs) (black bars) or human umbilical cord perivascular cells (HUCPVCs) (grey bars) towards CCM from HCC (HuH7 and HC-PT-5), hepatic stellate cells (LX-2), fibroblasts (WI-38) or endothelial cells (HMEC-1) was measured (FIG. **7**A). In each case, a higher migratory capacity towards all the CCM was found for HUCPVCs when compared to BM-MSCs. Moreover, in contrast to BM-MCSs, HUCPVCs showed capability to migrate to CCM derived from nontumoral components (fibroblast and endothelial cells).

Besides their capacity to migrate toward factors secreted by HCC, the arrest of MSCs within the microvasculature is considered a critical step for an efficient homing and anchorage to tumors. Therefore, cell adhesion assays were also performed as described in Example 1 to evaluate adhesion ability of MSCs. In that assay, HUCPVCs showed an increased in vitro adhesion to HMEC-1 endothelial cells in comparison with BM-MSCs (FIG. **7**B).

Example 8

HUCPVCs Presented In Vivo Migration Towards HCC Tumors

To further characterize MSC behavior in vivo, noninvasive migration assays were performed as described in Example 1. CM-DiI and DiR prelabelled BM-MSCs or HUCPVCs were i.v. injected in HCC tumor-bearing mice in order to evaluate MSC recruitment. Similar to our previous observation with BM-MSCs (FIG. **5**), at 3 days after cell transplantation a positive signal corresponding to HUCPVCs was found in liver, lungs, spleen, and s.c. tumors (FIG. **8**A). Despite the fact that total signal was lower in mice injected with HUCPVCs compared to those injected with BM-MSCs (FIG. **8**B), the percentage of total signal corresponding to s.c. tumor locations was increased in mice administered with HUCPVCs in comparison with animals that received BM-MSCs (FIGS. **8**C and **8**D), indicating an enhanced engrafiment of HUCPVCs into HCC tumors. In the other evaluated tissues, signal intensity was similar for BM-MSC or HUCPVCs in lung and liver and it was comparatively reduced in the spleen of HUCPVCs-injected mice (FIG. **8**D). Presence of MSCs in the s.c. tumors was also confirmed by fluorescence microscopy (Figure E). Finally, MSCs were evaluated for whether they might present differential migratory capacity towards CM obtained from s.c. tumors (TCM). A greater in vitro migratory capacity towards TCM from HCC was observed for HUCPVCs when compared to BM-MSCs (FIG. **8**F).

Example 9

Differential Expression of Cytokines/Chemokines Receptors and AMF/AAMFR Pathway in MSCs

In order to evaluate mechanisms partially explaining the differential migratory capacity of HUCPVCs compared to BM-MSCs towards tumor released factors, the expression of some chemokine receptors likely involved in MSC recruitment towards HCC was analyzed. Because interleukin- (IL-) 8, GRO, chemokine (C—C motif) ligand (CCL)-2, and IL-6 are among the most relevant factors in HCC (Bayo et al., Liver International 34(3):330-334 (2014)), qPCR (as described in Example 1) was used to evaluate the expression of CXCR1, CXCR2, CCR2, IL-6R, and IL-6ST. Constitutive CXCR1 and CXCR2 mRNA expression was found to be lower and CCR2 slightly higher in HUCPVCs when compared to BM-MSCs, while IL-6R and IL-6ST expression was similar in both MSCs sources (FIG. **9**A). Next, the axis of the autocrine motility factor (AMF) was evaluated. By qPCR, a significantly higher expression of the AMF receptor (AMFR) was found in HUCPVCs when compared to BM-MSCs. Similarly, genes known to be related to the availability of the receptor in the cell surface such as caveolin-1 (CAV-1) and caveolin-2 (CAV-2) were also highly expressed in HUCPVCs as well as the metalloproteinase 3 (MMP3), necessary to the transmigration process. In contrast, expression levels of insulin-like growth factor-binding protein 3 (IGFBP3), a protein that negatively regulates AMF/AMFR pathway, were found to be reduced in HUCPVCs when compared to BM-MSCs (FIG. **9**B).

Example 10

HUCPVCs Showed Enhanced Migration Towards AMF

The in vitro migration response to the recombinant AMF (rAMF) of both BM-MSCs (black bars) or HUCPVCs (grey bars) was tested using a chemotaxis assay (FIG. **10**A). A significantly higher migration to different doses of rAMF (0.5 and 0.75 μg/mL) was observed for HUCPVCs when compared to BM-MSCs. In spite of different types of MSCs showing similar reduction in migration levels (50% of control) towards HuH7 TCM after the blockage with anti-

AMF antibody (data not shown), preincubation of HC-PT-5 TCM with anti-AMF antibody (AMF-ab) resulted in a further reduction in HUCPVCs migration capacity (54% of control) when compared to BM-MSCs (67% of control) (FIG. **10**B).

Example 11

Anti-CXCR1, Anti-CXCR2, and Anti-MCP-1 Antibodies Inhibit MSC Migration

Blocking experiments were performed by preincubating TCM-HuH7 or TCM-HC-PT-5 with anti-HGF (10 μg/ml), anti-MCP-1 (10 μg/ml) or isotype control IgG for 1 hour. Similarly, anti-CXCR1 (10 μg/ml), anti-CXCR2 (10 μg/ml), both anti-CXCR1/anti-CXCR2, or isotype control IgG were pre-incubated with MSC for 1 hour. In vitro migration of MSCs towards TCM-HuH7 or TCM-HC-PT-5 were evaluated using the methods described in Example 1.

Antibody inhibition of CXCR1 or CXCR2 decreased MSC migration around 30% and incubation with both anti-CXCR1 and anti-CXCR2 antibodies inhibited migration around 40% (FIG. **11**A). Moreover, anti-MCP-1 inhibited MSC migration around 20%, but anti-HGF had no effect on MSC migration towards CM-HuH7 (FIG. **11**B).

Example 12

Migration of MSCs Engineered to Express Oncolytic Viruses Expressing Anti-Tumor Genes

MSCs will be engineered to express oncolytic virus expressing or not anti-tumor genes (including e.g., an interferon (e.g., interferon α, interferon β), an interleukin (e.g., interleukin 1, interleukin 12), a chemokine (e.g., CX3CL1), or a suicide gene (e.g., thymidine kinase, IL-12, IFN-gamma, TNF-alpha). First, MSCs will be infected in vitro at different MOIs (multiplicity of infection) ranging from 10 to 1000 in complete DMEM without SFB during 2 hours. Then, infected MSCs will be stimulated in culture with rAMF for about 18 h and systemically injected (5×10^5) in HCC, colorectal cancer, and/or breast cancer tumor-bearing mice. Tumor growth will be assessed by calliper and tumor volume (mm^3) will be calculated using the formula π/6× larger diameter×(smaller diameter)^2.

TABLE 1

Factors identified with the RayBio Human Cytokine Antibody Array 5 (Cat# AAH-CYT-5) in the TCM from samples 1 to 4, and their relative levels to positive control. Data are grouped according to the lane presented in the membrane.

		RayBio Human Cytokine Antibody Array 5			
Line		TCM sample 1	TCM sample 2	TCM sample 3	TCM sample 4
1	Pos	130.3	103.7	101.9	102.7
	Pos	122.2	103.5	94.0	95.9
	Pos	124.8	96.4	91.0	102.3
	Pos	105.0	96.4	91.1	99.1
	Neg	0.0	0.0	0.0	0.0
	Neg	0.0	0.0	0.0	0.0
	ENA-78	0.3	4.2	0.6	0.0
	GCSF	0.1	0.0	0.0	0.0
	GM-CSF	0.0	0.0	0.0	0.0
	Gro	16.1	4.2	11.1	51.0
	Gro-alpha	0.0	0.0	0.0	0.0
2	I-309	0.9	13.7	3.0	0.0
	IL-1alpha	2.4	3.1	3.4	0.0

TABLE 1-continued

Factors identified with the RayBio Human Cytokine Antibody Array 5 (Cat# AAH-CYT-5) in the TCM from samples 1 to 4, and their relative levels to positive control. Data are grouped according to the lane presented in the membrane.

		RayBio Human Cytokine Antibody Array 5			
Line		TCM sample 1	TCM sample 2	TCM sample 3	TCM sample 4
	IL-1beta	4.3	3.4	5.7	0.0
	IL-2	3.2	5.9	3.6	2.7
	IL-3	12.5	4.6	17.0	5.6
	IL-4	0.0	11.5	0.6	0.0
	IL-5	0.0	1.5	0.0	0.0
	IL-6	17.3	66.9	74.4	0.0
	IL-7	0.0	0.0	0.0	0.0
	IL-8	261.2	129.0	117.6	83.3
	IL-10	0.0	0.0	0.0	0.0
3	IL-12 p40p70	7.5	7.3	7.8	4.1
	IL-13	0.1	1.0	1.0	0.0
	IL-15	6.0	5.9	5.2	1.2
	IFN-GAMMA	12.6	7.6	7.6	4.7
	MCP-1	124.2	66.0	41.0	84.2
	MCP-2	1.2	2.8	4.3	0.0
	MCP-3	0.0	1.7	0.7	0.0
	MCSF	0.5	1.0	1.8	1.7
	MDC	0.4	0.0	0.2	0.0
	MIG	1.5	0.0	0.1	0.0
	MIP-1-beta	7.8	0.0	0.1	0.0
4	MIP-1-delta	1.6	7.0	5.4	0.0
	RANTES	9.6	11.4	8.5	3.2
	SCF	6.3	9.2	4.3	1.4
	SDF-1	3.8	4.5	2.5	1.5
	TARC	17.3	16.1	10.7	3.6
	TGF-beta1	5.5	6.1	4.2	2.0
	TNF-alpha	7.2	5.9	3.7	2.6
	TNF-beta	4.2	2.6	2.7	2.1
	EGF	0.9	0.5	2.4	1.5
	IGF-1	0.0	0.0	0.0	0.0
	Angiogenin	22.9	28.9	42.8	0.9
5	Oncostatin M	16.4	16.3	16.0	5.2
	Thrombopoietin	2.0	2.3	1.0	3.8
	VEGF	12.1	8.0	7.2	4.6
	PDGF-BB	13.3	8.6	6.4	2.8
	Leptin	12.2	6.8	5.5	2.4
	BDFN	25.0	11.9	16.1	8.0
	BLC	3.2	3.2	2.6	2.2
	Ck beta 8-1	4.3	2.7	1.6	1.7
	Eotaxin	1.9	1.5	2.3	2.4
	Eotaxin-2	0.3	0.0	0.0	0.0
	Eotaxin-3	0.0	0.0	0.0	1.1
6	FGF-4	6.6	5.1	7.6	2.4
	FGF-6	10.2	7.7	5.0	1.5
	FGF-7	4.4	2.6	2.7	0.8
	FGF-9	16.9	9.2	7.4	5.0
	Flt-3 Ligand	4.2	2.2	1.3	1.5
	Fractalkine	4.3	2.4	1.4	2.1
	GCP-2	2.6	2.3	0.8	1.9
	GDNF	7.0	3.4	2.9	5.5
	HGF	0.1	0.0	74.2	0.0
	IGFBP-1	6.9	0.0	71.6	0.0
	IGFBP-2	5.4	0.0	25.7	10.0
7	IGFBP-3	7.5	7.4	9.1	2.8
	IGFBP-4	3.0	1.3	1.6	0.6
	IL-16	11.7	12.7	9.4	1.0
	IP-10	27.3	11.3	1.8	5.3
	LIF	32.4	10.6	52.6	6.8
	LIGHT	5.0	1.3	12.6	1.5
	MCP-4	0.8	13.0	13.0	0.0
	MIF	45.4	0.3	0.9	29.4
	MIP-3 alpha	0.0	0.0	21.0	8.6
	NAP-2	7.7	0.0	75.1	2.3
	NT-3	5.6	0.0	28.2	5.6
8	NT-4	1.1	1.6	2.3	0.0
	Osteopontin	12.4	11.9	41.8	3.0
	osteoprotegerin	8.0	3.8	9.7	0.0
	PARC	4.3	1.2	0.5	0.0
	PIGF	0.2	0.0	0.0	0.0
	TGF-beta 2	27.2	7.7	12.7	11.2

TABLE 1-continued

Factors identified with the RayBio Human Cytokine Antibody Array 5 (Cat# AAH-CYT-5) in the TCM from samples 1 to 4, and their relative levels to positive control. Data are grouped according to the lane presented in the membrane.

	RayBio Human Cytokine Antibody Array 5			
Line	TCM sample 1	TCM sample 2	TCM sample 3	TCM sample 4
TGF-beta 3	1.6	0.0	0.3	1.8
TIMP-1	31.4	9.4	21.7	36.5
TIMP-2	0.0	0.0	8.1	16.1
POS	69.6	0.0	112.8	72.8
POS	48.3	0.0	109.3	66.3

TABLE 2

Factors identified with the RayBio Human Chemokine Antibody array 1 (Cat# AAH-CHE-1) in the TCM from samples 3 and 4, and their relative levels to positive control. Data are presented as the average of the dot and grouped according to the lane presented in the membrane.

		RayBio Human Chemokine antibody array 1	
Line		TCM sample 3	TCM sample 4
1 and 2 Average	POS	100.01	102.48
	POS	95.86	110.67
	NEG	0.00	0.00
	NEG	0.00	0.00
	BCL	0.00	0.00
	CCL28	0.00	0.00
	Ck beta 8-1	0.00	0.00
	CTACK	0.00	0.00
	CXCL16	0.00	0.00
	ENA78	0.00	0.00
	Eotaxin	0.00	0.00
	Eotaxin-2	0.00	0.00
3 and 4 Average	Eotaxin-3	3.81	0.00
	Fractalkine	2.65	0.00
	GCP-2	1.58	0.00

TABLE 2-continued

Factors identified with the RayBio Human Chemokine Antibody array 1 (Cat# AAH-CHE-1) in the TCM from samples 3 and 4, and their relative levels to positive control. Data are presented as the average of the dot and grouped according to the lane presented in the membrane.

		RayBio Human Chemokine antibody array 1	
Line		TCM sample 3	TCM sample 4
	GRO	139.84	107.13
	GRO-alpha	5.58	9.76
	HCC-4	0.00	0.00
	I-309	0.00	0.00
	I-TAC	0.00	0.00
	IL-8	157.61	72.43
	Ip-10	5.38	3.92
	Lymphotactin	0.00	0.00
	MCP-1	6.54	30.94
5 and 6 Average	MCP-2	1.04	0.00
	MCP-3	0.59	0.00
	MCP-4	0.43	0.00
	MDC	2.13	0.00
	MIG	6.81	0.00
	MIP-1alpha	1.47	0.00
	MIP-1beta	5.16	2.41
	MIP-1delta	2.03	0.00
	MIP-3alpha	2.40	8.38
	MIP-3beta	0.00	0.00
	MPIF-1	0.00	0.00
	NAP-2	57.44	0.00
7 and 8 Average	PARC	0.68	0.00
	RANTES	3.16	0.00
	SDF-1 alpha	1.01	0.00
	SDF-1 beta	0.68	0.00
	TARC	0.00	0.00
	TECK	0.00	0.00
	BLANK	0.00	0.00
	BLANK	0.00	0.00
	BLANK	0.00	0.00
	BLANK	0.00	0.00
	POS	0.00	0.00
	POS	108.86	77.72

TABLE 3

445 genes differentially expressed in MSC non-exposed in comparison with cells exposed to TCM from sample 1 in comparison with non-exposed cells. The magnitude of the expression change is represented as the logarithm of the fold change.

	GeneID	Name	Description	PValue	Log2FC
1	11137	PWP1	PWP1 homolog (*S. cerevisiae*)	0.004	−0.409
2	100133941	CD24	CD24 molecule	0.005	0.448
3	1968	EIF2S3	eukaryotic translation initiation factor 2, subunit 3 gamma, 52 kDa	0.047	−0.368
4	386679	KRTAP10-2	keratin associated protein 10-2	0.016	−0.519
5	6782	HSPA13	heat shock protein 70 kDa family, member 13	0.018	−0.52
6	817	CAMK2D	calcium/calmodulin-dependent protein kinase II delta	0.039	−0.379
7	81626	SHCBP1L	SHC SH2-domain binding protein 1-like	0.016	0.375
8	51278	IER5	immediate early response 5	<0.001	0.873
9	54541	DDIT4	DNA-damage-inducible transcript 4	0.007	0.349
10	2199	FBLN2	fibulin 2	0.001	0.491
11	3488	IGFBP5	insulin-like growth factor binding protein 5	0.023	0.306
12	57104	PNPLA2	patatin-like phospholipase domain containing 2	0.033	0.957
13	10659	CELF2	CUG8P, Elav-like family member 2	0.004	0.538
14	50613	UBQLN3	ubiquilin 3	0.034	0.335
15	6396	SEC13	SEC13 homolog (*S. cerevisiae*)	0.047	−0.32
16	8624	PSMG1	proteasome (prosome, macropain) assembly chaperone 1	0.008	0.481
17	51310	SLC22A17	solute carrier family 22, member 17	0.048	0.232
18	5066	PAM	peptidylglycine alpha-amidating monooxygenase	0.027	−0.427
19	10938	EHD1	EH-domain containing 1	0.021	0.427
20	10777	ARPP21	cAMP-regulated phosphoprotein, 21 kDa	0.025	−0.331
21	51727	CMPK1	cytidine monophosphate (UMP-CMP) kinase 1, cytosolic	0.046	−0.294
22	56951	C5orf15	chromosome 5 open reading frame 15	0.026	0.305
23	3954	LETM1	leucine zipper-EF-hand containing transmembrane protein 1	0.007	−0.363
24	7278	TUBA3C	tubulin, alpha 3c	0.007	0.323

TABLE 3-continued

445 genes differentially expressed in MSC non-exposed in comparison with cells exposed to TCM from sample 1 in comparison with non-exposed cells. The magnitude of the expression change is represented as the logarithm of the fold change.

	GeneID	Name	Description	PValue	Log2FC
25	2574	GAGE2C	G antigen 2C	0.001	0.546
26	10476	ATP5H	ATP synthase, H+ transporting, mitochandrial Fo complex, subunit d	0.025	−0.361
27	7323	U8E2D3	ubiquitin-conjugating enzyme E2D 3 (U8C4/5 homolog, yeast)	0.037	0.289
28	29893	PSMC3IP	PSMC3 interacting protein	0.034	0.281
29	8404	SPARCL1	SPARC-like 1 (hevin)	0.025	0.472
30	55062	WIPI1	WD repeat domain, phosphoinositide interacting 1	0.03	−0.391
31	55907	CMAS	cytidine monophosphate N-acetylneuraminic acid synthetase	0.048	0.317
32	84661	DPY30	dpy-30 homolog (*C. elegans*)	0.05	0.368
33	55000	TUG1	taurine unregulated 1 (non-protein coding)	0.014	0.48
34	4809	NHP2L1	NHP2 non-histone chromosome protein 2-like 1 (*S. cerevisiae*)	0.042	0.313
35	1672	DEFB1	defensin, beta 1	0.004	0.53
36	10769	PLK2	polo-like kinase 2	0.033	0.348
37	2191	FAP	fibroblast activation protein, alpha	0.009	−0.403
38	1634	DCN	decorin	0.015	−0.248
39	4779	NFE2L1	nuclear factor (erythroid-derived 2)-like 1	0.013	0.281
40	386677	KRTAP10-1	keratin associated protein 10-1	0.039	−0.271
41	1912	PHC2	polyhomeotic homolog 2 (*Drosophila*)	0.033	−0.502
42	100271071	RPS17P10	ribosomal protein S17 pseudogene 10	0.025	−0.514
43	7184	HSP90B1	heat shock protein 90 kDa beta (Grp94), member 1	0.039	0.348
44	10961	ERP29	endoplasmic reticulum protein 29	0.022	0.365
45	7117	TMSL3	thymosin-like 3	0.04	−0.285
46	283131	NEAT1	nuclear paraspeckle assembly transcript 1 (non-protein coding)	0.013	−0.584
47	467	ATF3	activating transcription factor 3	<0.001	1.057
48	51322	WAC	WW domain containing adaptor with coiled-coil	0.006	0.504
49	54600	UGT1A9	UDP glucuronosyltransferase 1 family, polypeptide A9	0.042	0.313
50	8653	DDX3Y	DEAD (Asp-Glu-Ala-Asp) box polypeptide 3, Y-linked	0.015	−0.589
51	89941	RHOT2	ras homolog gene family, member T2	0.024	−0.315
52	64855	FAM1298	family with sequence similarity 129, member B	0.043	−0.278
53	10135	NAMPT	nicotinamide phosphoribosyltransferase	0.029	−0.493
54	51460	SFMBT1	Scm-like with four mbt domains 1	0.044	0.366
55	8778	SIGLEC5	sialic acid binding Ig-like lectin 5	0.043	−0.345
56	200185	KRTCAP2	keratinocyte associated protein 2	0.017	−0.294
57	3295	HSD17B4	hydroxysteroid (17-beta) dehydrogenase 4	0.026	−0.432
58	58515	SELK	selenoprotein K	0.009	0.302
59	4097	MAFG	v-maf musculoaponeurotic fibrosarcoma oncogene homolog G (avian)	0.022	0.281
60	51071	DERA	deoxyribose- phosphate aldolase (putative)	0.023	0.275
61	11149	BVES	blood vessel epicardial substance	0.027	0.281
62	10808	HSPH1	heat shock 105 kDa/110 kDa protein 1	<0.001	1.029
63	56110	PCDHGA5	protocadherin gamma subfamily A, 5	0.045	−0.278
64	4758	NEU1	sialidase 1 (lysosomal sialidase)	0.003	0.439
65	4627	MYH9	myosin, heavy chain 9, non-muscle	0.048	−0.243
66	2323	FLT3LG	fms-related tyrosine kinase 3 ligand	0.026	−0.363
67	23218	NBEAL2	neurobeachin-like 2	0.007	−0.276
68	1003	CDH5	cadherin 5, type 2 (vascular endothelium)	0.04	0.486
69	9531	BAG3	BCL2-associated athanogene 3	<0.001	0.69
70	51726	DNAJB11	DnaJ (Hsp40) homolog, subfamily B, member 11	<0.001	0.514
71	8878	SQSTM1	sequestosome 1	0.047	0.241
72	10963	STIP1	stress-induced-phosphoprotein 1	0.044	0.352
73	478	ATP1A3	ATPase, Na+/K+ transporting, alpha 3 polypeptide	0.013	0.545
74	338799	LOC338799	hypothetical LOC338799	0.043	−0.307
75	5476	CTSA	cathepsin A	0.033	−0.261
76	158056	MAMDC4	MAM domain containing 4	0.008	−0.474
77	533	ATP6V0B	ATPase, H+ transporting, lysosomal 21 kDa, V0 subunit b	0.05	0.31
78	3313	HSPA9	heat shock 70 kDa protein 9 (mortalin)	0.034	0.308
79	2578	GAGE6	G antigen 6	0.038	0.389
80	6125	RPL5	ribosomal protein L5	0.01	−0.392
81	3336	HSPE1	heat shock 10 kDa protein 1 (chaperonin 10)	0.003	0.526
82	80279	CDKSRAP3	CDKS regulatory subunit associated protein 3	0.004	0.418
83	5707	PSMD1	proteasome (prosome, macropain) 26S subunit, non-ATPase, 1	0.044	0.3
84	57222	ERGIC1	endoplasmic reticulum-goigi intermediate compartment (ERGIC) 1	0.036	−0.321
85	8566	PDXK	pyridoxal (pyridoxine, vitamin B6) kinase	0.003	0.441
86	3703	STT3A	STT3, subunit of the oligosaccharyltransferase complex, homolog A (*S. cerevisiae*)	0.037	−0.283
87	4884	NPTX1	neuronal pentraxin I	0.041	0.393
88	5573	PRKAR1A	protein kinase, cAMP-dependent, regulatory, type I, alpha (tissue specific extinguisher 1)	0.009	−0.612
89	3397	ID1	Inhibitor of DNA binding 1, dominant negative helix-loop-helix protein	0.032	0.236
90	57677	ZFP14	zinc finger protein 14 homolog (mouse)	0.047	0.334
91	53826	FXYD6	FXYD domain containing ion transport regulator 6	0.035	0.282
92	1164	CKS2	CDC28 protein kinase regulatory subunit 2	<0.001	0.454
93	7120	TMSL6	thymosin-like 6 (pseudogene)	0.034	−0.312
94	4673	NAP1L1	nucleosome assembly protein 1-like 1	0.01	0.342

TABLE 3-continued

445 genes differentially expressed in MSC non-exposed in comparison with cells exposed to TCM from sample 1 in comparison with non-exposed cells. The magnitude of the expression change is represented as the logarithm of the fold change.

	GeneID	Name	Description	PValue	Log2FC
95	23621	BACE1	beta-site APP-cleaving enzyme 1	0.005	−0.416
96	8424	BBOX1	butyrobetaine (gamma), 2-oxoglutarate dioxygenase (gamma-butyrobetaine hydroxylase) 1	0.04	0.365
97	56944	OLFML3	olfactomedin-like 3	0.003	−0.338
98	51081	MRPS7	mitochondrial ribosomal protein S7	0.007	0.304
99	665	BNIP3L	BCL2/adenovirus E1B 19 kDa interacting protein 3-like	0.025	−0.295
100	3032	HADHB	hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase (trifunctional protein), beta subunit	0.012	−0.313
101	3301	DNAJA1	DnaJ (Hsp40) homolog, subfamily A, member 1	<0.001	0.624
102	9315	C5orf13	chromosome 5 open reading frame 13	0.013	−0.266
103	468	ATF4	activating transcription factor 4 (tax-responsive enhancer element B67)	0.009	0.29
104	91624	NEXN	nexilin (F actin binding protein)	0.048	0.243
105	5358	PLS3	plastin 3	0.015	−0.448
106	23603	CORO1C	coronin, actin binding protein, 1C	0.03	−0.306
107	813	CALU	calumenin	0.017	−0.457
108	6046	BRD2	bromodomain containing 2	0.022	0.336
109	25879	DCAF13	DDB1 and CUL4 associated factor 13	0.05	0.394
110	6390	SDHB	succinate dehydrogenase complex, subunit B, iron sulfur (Ip)	0.001	0.414
111	26528	DAZAP1	DAZ associated protein 1	0.032	0.376
112	54504	CPVL	carboxypeptidase, vitellogenic-like	0.016	0.344
113	7058	THBS2	thrombospondin 2	0.026	−0.325
114	2131	EXT1	exostosin 1	0.007	−0.444
115	65055	REEP1	receptor accessory protein 1	0.012	0.371
116	90701	SEC11C	SEC11 homolog C (*S. cerevisiae*)	0.018	0.407
117	71	ACTG1	actin, gamma 1	0.022	−0.296
118	84681	HINT2	histidine triad nucleotide binding protein 2	0.013	0.382
119	79048	SECISBP2	SECIS binding protein 2	0.017	−0.332
120	231	AKR1B1	aldo-keto reductase family 1, member B1 (aldose reductase)	0.027	−0.268
121	501	ALDH7A1	aldehyde dehydrogenase 7 family, member A1	0.007	−0.424
122	84545	MRPL43	mitochondrial ribosomal protein L43	0.007	−0.509
123	4358	MPV17	MpV17 mitochondrial inner membrane protein	0.015	−0.355
124	103	ADAR	adenosine deaminase, RNA-specific	0.035	0.344
125	961	CD47	CD47 molecule	0.024	−0.518
126	54881	TEX10	testis expressed 10	0.023	−0.339
127	7072	TIA1	TIA1 cytotoxic granule-associated RNA binding protein	0.025	−0.482
128	11217	AKAP2	A kinase (PRKA) anchor protein 2	0.041	−0.275
129	5431	POLR2B	polymerase (RNA) II (DNA directed) polypeptide B, 140 kDa	0.038	−0.26
130	84817	TXNDC17	thioredoxin domain containing 17	0.012	0.396
131	8829	NRP1	neuropilin 1	0.015	−0.389
132	79096	C11orf49	chromosome 11 open reading frame 49	0.046	−0.331
133	1164	CKS2	CDC28 protein kinase regulatory subunit 2	<0.001	0.363
134	10146	G3BP1	GTPase activating protein (SH3 domain) binding protein 1	0.033	0.315
135	5690	PSMB2	proteasome (prosome, macropain) subunit, beta type, 2	0.047	−0.233
136	81688	C6orf62	chromosome 6 open reading frame 62	0.001	0.359
137	54658	UGT1A1	UDP glucuronosyltransferase 1 family, polypeptide A1	0.049	0.257
138	65009	NDRG4	NDRG family member 4	0.043	0.241
139	387707	CC2D2B	coiled-coil and C2 domain containing 2B	0.037	0.287
140	54840	APTX	aprataxin	0.025	0.339
141	29995	LMCD1	LIM and cysteine-rich domains 1	0.049	−0.406
142	9354	U8E4A	ubiquitination factor E4A (UFD2 homolog, yeast)	0.036	−0.379
143	1435	CSF1	colony stimulating factor 1 (macrophage)	0.011	−0.445
144	390714	LOC390714	similar to Ig heavy chain V-III region VH26 precursor	0.02	−0.272
145	3337	DNAJB1	DnaJ (Hsp40) homolog, subfamily B, member 1	<0.001	0.442
146	51023	MRPS18C	mitochondrial ribosomal protein S18C	0.03	0.3
147	2171	FABP5	fatty acid binding protein 5 (psoriasis-associated)	0.006	0.369
148	653450	FAM21D	family with sequence similarity 21, member D	0.044	0.261
149	4054	LTBP3	latent transforming growth factor beta binding protein 3	0.017	−0.863
150	2619	GAS1	growth arrest-specific 1	<0.001	−0.547
151	25	ABL1	c-abl oncogene 1, non-receptor tyrosine kinase	0.023	−0.261
152	51655	RASD1	RAS, dexamethasone-induced 1	0.027	−0.319
153	83955	NACAP1	nascent-polypeptide-associated complex alpha polypeptide pseudogene 1	0.034	−0.35
154	9689	BZW1	basic leucine zipper and W2 domains 1	0.017	−0.277
155	900	CCNG1	cyclin G1	0.012	−0.317
156	387763	C11orf96	chromosome 11 open reading frame 96	<0.001	0.589
157	7955	STL	six-twelve leukemia	0.031	0.629
158	7873	MANF	mesencephalic astrocyte-derived neurotrophic factor	0.004	0.417
159	51714	SELT	selenoprotein T	0.027	0.25
160	3476	IGBP1	immunoglobulin (CD79A) binding protein 1	0.005	−0.397
161	10370	CITED2	Cbp/p300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain, 2	0.048	−0.328
162	84886	C1orf198	chromosome 1 open reading frame 198	0.003	−0.395
163	1490	CTGF	connective tissue growth factor	0.01	−0.395

TABLE 3-continued

445 genes differentially expressed in MSC non-exposed in comparison with cells exposed to TCM from sample 1 in comparison with non-exposed cells. The magnitude of the expression change is represented as the logarithm of the fold change.

	GeneID	Name	Description	PValue	Log2FC
164	6734	SRPR	signal recognition particle receptor (docking protein)	0.035	−0.238
165	79594	MUL1	mitochondral E3 ubiquitin protein ligase 1	0.022	0.434
166	9181	ARHGEF2	Rho/Rac guanine nucleotide exchange factor (GEF) 2	0.018	0.27
167	55695	NSUN5	NOP2/Sun domain family, member 5	0.023	0.268
168	5937	RBMS1	RNA binding motif, single stranded interacting protein 1	0.001	−0.447
169	3312	HSPA8	heat shock 70 kDa protein 8	0.007	0.316
170	127933	UHMK1	U2AF homology motif (UHM) kinase 1	0.037	−0.251
171	25978	CHMP2B	chromatin modifying protein 2B	0.035	−0.356
172	8553	BHLHE40	basic helix-loop-helix family, member e40	<0.001	0.629
173	79770	TXNDC15	thioredoxin domain containing 15	0.048	−0.302
174	10079	ATP9A	ATPase, class II, type 9A	0.039	−0.277
175	5045	FURIN	furin (paired basic amino acid cleaving enzyme)	0.019	−0.398
176	267	AMFR	autocrine motility factor receptor	0.024	−0.316
177	3827	KNG1	kininogen 1	0.016	−0.464
178	5682	PSMA1	proteasome (prosome, macropain) subunit, alpha type, 1	0.047	−0.213
179	57449	PLEKHG5	pleckstrin homology domain containing, family G (with RhoGef domain) member 5	0.025	−0.255
180	441204	LOC441204	hypothetical locus LOC441204	0.024	−0.464
181	23654	PLXNB2	plexin B2	0.022	−0.289
182	2745	GLRX	glutaredoxin (thioltransferase)	0.009	0.352
183	2939	GSTA2	glutathione S-transferase alpha 2	0.006	0.493
184	29968	PSAT1	phosphoserine aminotransferase 1	0.014	0.42
185	151579	BZW1P2	basic leucine zipper and W2 domains 1 pseudogene 2	<0.001	−0.517
186	11079	RER1	RER1 retention in endoplasmic reticulum 1 homolog (*S. cerevisiae*)	0.044	−0.247
187	115207	KCTD12	potassium channel tetramerisation domain containing 12	<0.001	−0.632
188	283711	LOC283711	ubiquitin-conjugating enzyme E2C pseudogene	0.041	0.323
189	3225	HOXC9	homeobox C9	0.05	0.333
190	1348	COX7A2P2	cytochrome c oxidase subunit VIIa polypeptide 2 (liver) pseudogene 2	0.044	0.277
191	442454	LOC442454	ubiquinol-cytochrome c reductase binding protein pseudogene	0.028	−0.389
192	4553	TRNA	tRNA	<0.001	0.882
193	55002	TMCO3	transmembrane and coiled-coil domains 3	0.005	−0.34
194	4853	NOTCH2	notch 2	0.031	−0.294
195	10133	OPTN	optineurin	0.028	0.224
196	51533	PHF7	PHD finger protein 7	0.024	0.263
197	3322	HSP90AA3P	heat shock protein 90 kDa alpha (cytosolic), class A member 3 (pseudogene)	0.002	0.481
198	345645	LOC345645	proteasome (prosome, macropain) 26S subunit, ATPase, 1 pseudogene	0.034	0.319
199	5934	RBL2	retinoblastoma-like 2 (p130)	0.025	−0.372
200	29080	CCDC59	coiled-coil domain containing 59	0.011	0.464
201	3032	HADHB	hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase (trifunctional protein), beta subunit	0.038	−0.211
202	51339	DACT1	dapper, antagonist of beta-catenin, homolog 1 (*Xenopus laevis*)	0.011	−0.4
203	5550	PREP	prolyl endopeptidase	<0.001	−0.499
204	2581	GALC	galactosylceramidase	0.02	−0.59
205	4311	MME	membrane metallo-endopeptidase	0.009	−0.337
206	28970	C11orf54	chromosome 11 open reading frame 54	0.012	0.398
207	196500	C12orf53	chromosome 12 open reading frame 53	0.024	−0.482
208	51191	HERC5	hect domain and RLD 5	0.004	0.472
209	84270	C9orf89	chromosome 9 open reading frame 39	0.018	−0.268
210	9672	SDC3	syndecan 3	0.023	0.239
211	84445	LZTS2	leucine zipper, putative tumor suppressor 2	0.031	0.256
212	1528	CYB5A	cytochrome b5 type A (microsomal)	0.011	0.443
213	7316	UBC	ubiquitin C	<0.001	0.512
214	10576	CCT2	chaperonin containing TCP1, subunit 2 (beta)	0.037	0.397
215	401967	N8PF17P	neuroblastoma breakpoint family, member 17 (pseudogene)	0.034	0.347
216	441198	LOC441198	similar to Heat shock cognate 71 kDa protein	0.031	0.284
217	29982	NRBF2	nuclear receptor binding factor 2	0.003	0.317
218	9082	XKRY	XK, Kell blood group complex subunit-related, Y-linked	0.038	0.276
219	3856	KRT8	keratin 8	0.033	0.28
220	349114	NCRNA00265	non-protein coding RNA 265	0.031	0.331
221	10961	ERP29	endoplasmic reticulum protein 29	0.019	0.334
222	1305	COL13A1	collagen, type XIII, alpha 1	0.007	0.365
223	3304	HSPA1B	heat shock 70 kDa protein 1B	<0.001	0.816
224	80255	SLC35F5	solute carrier family 35 member F5	0.039	−0.307
225	84791	C1orf97	chromosome 1 open reading frame 97	0.013	0.345
226	91012	LASS5	LAG1 homolog, ceramide synthase 5	0.034	−0.327
227	124446	TMEM219	transmembrane protein 219	0.027	0.27
228	63908	NAPB	N-ethylmaleimide-sensitive factor attachment protein, beta	0.013	0.328
229	6590	SLPI	secretory leukocyte peptidase inhibitor	0.026	0.261
230	144110	TMEM86A	transmembrane protein 86A	0.018	0.375
231	9326	ZNHIT3	zinc finger, HIT-type containing 3	0.046	−0.276
232	9719	ADAMTSL2	ADAMTS-like 2	0.039	0.306

TABLE 3-continued

445 genes differentially expressed in MSC non-exposed in comparison with cells exposed to TCM from sample 1 in comparison with non-exposed cells. The magnitude of the expression change is represented as the logarithm of the fold change.

	GeneID	Name	Description	PValue	Log2FC
233	84866	TMEM25	transmembrane protein 25	<0.001	−0.5
234	340198	IFITM4P	interferon induced transmembrane protein 4 pseudogene	0.043	0.351
235	253832	ZDHHC20	zinc finger, DHHC-type containing 20	0.038	−0.328
236	284672	LOC284672	prostaglandin E synthase 3 (cytosolic) pseudogene	0.009	0.303
237	376497	SLC27A1	solute carrier family 27 (fatty acid transporter), member 1	0.002	−0.5
238	51510	CHMP5	chromatin modifying protein 5	0.004	0.335
239	4282	MIF	macrophage migration inhibitory factor (glycosylation-inhibiting factor)	0.035	−0.203
240	65110	UPF3A	UPF3 regulator of nonsense transcripts homolog A (yeast)	0.031	0.381
241	83999	KREMEN1	kringle containing transmembrane protein 1	0.049	0.263
242	5412	UBL3	ubiquitin-like 3	0.038	−0.323
243	391356	C2orf79	chromosome 2 open reading frame 79	0.049	0.229
244	6890	TAP1	transporter 1, ATP-binding cassette, sub-family B (MDR/TAP)	0.005	0.318
245	388581	FAM132A	family with sequence similarity 132, member A	0.009	0.364
246	22936	ELL2	elongation factor, RNA polyrnerase II, 2	0.002	−0.411
247	55138	FAM90A1	family with sequence similarity 90, member A1	0.03	0.313
248	10252	SPRY1	sprouty homolog 1, antagonist of FGF signaling (*Drosophila*)	0.007	−0.439
249	1827	RCAN1	regulator of calcineurin 1	<0.001	−0.69
250	345757	FAM174A	family with sequence similarity 174, member A	0.026	−0.257
251	3434	IFIT1	interferon-induced protein with tetratricopeptide repeats 1	<0.001	0.471
252	26160	IFT172	intraflagellar transport 172 homolog (*Chlamydomonas*)	0.018	0.299
253	51019	CCDC53	coiled-coil domain containing 53	0.032	0.314
254	1845	DUSP3	dual specificity phosphatase 3	0.015	0.375
255	51569	UFM1	ubiquitin-fold modifier 1	0.034	0.478
256	400	ARL1	ADP-ribosylation factor-like 1	0.032	−0.499
257	7177	TPSAB1	tryptase alpha/beta 1	0.042	0.244
258	1213	CLTC	clathrin, heavy chain (Hc)	0.034	0.291
259	283070	LOC283070	hypothetical LOC283070	0.032	0.339
260	5217	PFN2	profilin 2	0.016	−0.266
261	55818	KDM3A	lysine (K)-specific demethylase 3A	0.003	0.44
262	51652	VPS24	vacuolar protein sorting 24 homolog (*S. cerevisiae*)	0.007	0.347
263	994	CDC25B	cell division cycle 25 homolog B (*S. pombe*)	0.006	0.456
264	4170	MCL1	myeloid cell leukemia sequence 1 (BCL2-related)	0.001	0.417
265	1593	CYP27A1	cytochrome P450, family 27, subfamily A, polypeptide 1	0.042	−0.312
266	10123	ARL4C	ADP-ribosylation factor-like 4C	0.003	0.437
267	83658	DYNLRB1	dynein, light chain, roadblock-type 1	0.035	−0.318
268	516	ATP5G1	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit C1 (subunit 9)	0.012	−0.396
269	3324	HSP90AA2	heat shock protein 90 kDa alpha (cytosolic), class A member 2	<0.001	0.608
270	57092	PCNP	PEST proteolytic signal containing nuclear protein	0.006	−0.394
271	4499	MT1M	metallothionein 1M	0.013	0.349
272	2745	GLRX	glutaredoxin (thioltransferase)	<0.001	0.783
273	23559	WBP1	WW domain binding protein 1	0.032	−0.261
274	4048	LTA4H	leukotriene A4 hydrolase	0.046	−0.344
275	23210	JMJD6	jumonji domain containing 6	0.017	−0.272
276	5578	PRKCA	protein kinase C, alpha	0.032	−0.384
277	54538	ROBO4	roundabout homolog 4, magic roundabout (*Drosophila*)	0.035	0.371
278	260436	C4orf7	chromosome 4 open reading frame 7	0.01	0.437
279	7280	TUBB2A	tubulin, beta 2A	0.018	0.313
280	286157	PCBP2P2	poly(rC) binding protein 2 pseudogene 2	0.023	−0.224
281	4499	MT1M	metallothionein 1M	<0.001	0.415
282	284861	LOC284861	hypothetical LOC284861	0.044	0.439
283	10159	ATP6AP2	ATPase, H+ transporting, lysosomail accessory protein 2	0.032	−0.376
284	8522	GAS7	growth arrest-specific 7	0.026	−0.272
285	3930	LBR	lamin B receptor	0.034	0.388
286	51645	PPIL1	peptidylprolyl isomerase (cyclophilin)-like 1	0.04	0.309
287	23174	ZCCHC14	zinc finger, CCHC domain containing 14	0.006	0.396
288	23451	SF3B1	splicing factor 3b, subunit 1, 155 kDa	0.029	−0.245
289	604	BCL6	B-cell CLL/lymphoma 6	0.023	−0.452
290	8537	BCAS1	breast carcinoma amplified sequence 1	0.015	0.337
291	5522	PPP2R2C	protein phosphatase 2, regulatory subunit B, gamma	0.01	0.306
292	4567	TRNL1	tRNA	0.014	0.375
293	1073	CFL2	cofilin 2 (muscle)	0.015	−0.357
294	30001	ERO1L	ERO1-like (*S. cerevisiae*)	0.021	0.459
295	115207	KCTD12	potassium channel tetramerisation domain containing 12	0.01	−0.527
296	201595	STT3B	STT3, subunit of the oligosaccharyltransferase complex, homolog B (*S. cerevisiae*)	0.04	0.325
297	3303	HSPA1A	heat shock 70 kDa protein 1A	<0.001	1.471
298	4314	MMP3	matrix metallopeptidase 3 (stromelysin 1, progelatinase)	0.013	0.48
299	10628	TXNIP	thioredoxin interacting protein	<0.001	−0.817
300	2137	EXTL3	exostoses (multiple)-like 3	0.028	0.335
301	9636	ISG15	ISG15 ubiquitin-like modifier	0.001	1.023
302	7207	TRNAL1	transfer RNA leucine 1 (anticodon AAG)	0.005	0.371
303	2876	GPX1	glutathione peroxidase 1	0.029	−0.232

TABLE 3-continued

445 genes differentially expressed in MSC non-exposed in comparison with cells exposed to TCM from sample 1 in comparison with non-exposed cells. The magnitude of the expression change is represented as the logarithm of the fold change.

	GeneID	Name	Description	PValue	Log2FC
304	9709	HERPUD1	homocysteine-inducible, endoplasmic reticulum stress-inducible, ubiquitin-like domain member 1	<0.001	0.58
305	56034	PDGFC	platelet derived growth factor C	0.049	−0.241
306	123811	FOPNL	FGFR1OP N-terminal like	0.022	−0.291
307	55827	DCAF6	DDB1 and CUL4 associated factor 6	0.021	0.301
308	81894	SLC25A28	solute carrier family 25, member 28	0.002	0.336
309	5654	HTRA1	HtrA serine peptidase 1	0.028	−0.478
310	6652	SORD	sorbitol dehydrogenase	0.047	0.321
311	402562	HNRNPA1P8	heterogeneous nuclear ribonucleoprotein A1 pseudogene 8	0.017	−0.324
312	6428	SRSF3	serine/arginine-rich splicing factor 3	<0.001	0.468
313	55920	RCC2	regulator of chromosome condensation 2	0.01	0.322
314	79600	TCTN1	tectonic family member 1	0.026	0.306
315	433	ASGR2	asialoglycoprotein receptor 2	0.015	0.306
316	9510	ADAMTS1	ADAM metallopeptidase with thrombospondin type 1 motif, 1	0.002	−0.542
317	7754	ANF204P	zinc finger protein 204, pseudogene	0.02	0.314
318	11098	PRSS23	protease, serine, 23	0.019	0.333
319	79174	CRELD2	cysteine-rich with EGF-like domains 2	0.004	0.496
320	7453	WARS	tryptophanyl-tRNA synthetase	0.024	0.396
321	51660	BRP44L	brain protein 44-like	0.014	0.393
322	7307	U2AF1	U2 small nuclear RNA auxiliary factor 1	0.038	0.245
323	7358	UGDH	UDP-glucose 6-dehydrogenase	0.02	0.373
324	2743	GLRB	glycine receptor, beta	0.03	0.272
325	7180	CRISP2	cysteine-rich secretory protein 2	0.009	0.445
326	9728	SECISBP2L	SECIS binding protein 2-like	0.047	−0.284
327	9467	SH3BP5	SH3-domain binding protein 5 (BTK-associated)	0.006	0.394
328	9246	UBE2L6	ubiquitin-conjugating enzyme E2L 6	<0.001	0.561
329	6236	RRAD	Ras-related associated with diabetes	<0.001	0.756
330	114822	RHPN1	rhophilin, Rho GTPase binding protein 1	0.01	−0.268
331	55752	sep-11	septin 11	0.028	0.419
332	91614	DEPDC7	DEP domain containing 7	0.041	−0.251
333	3207	HOXA11	homeobox A11	0.009	0.66
334	116254	C6orf72	chromosome 6 open reading frame 72	0.006	−0.306
335	51187	RSL24D1	ribosomal L24 domain containing 1	0.042	−0.253
336	10728	PTGES3	prostaglandin E synthase 3 (cytosolic)	0.012	0.279
337	284361	C19orf63	chromosome 19 open reading frame 63	0.043	0.271
338	143689	PIWIL4	piwi-like 4 (*Drosophila*)	0.001	0.525
339	85363	TRIM5	tripartite motif containing 5	0.005	0.373
340	9520	NPEPPS	aminopeptidase puromycin sensitive	0.005	−0.352
341	29880	ALG5	asparagine linked glycosylation 5, dolichyl-phosphate beta-glucosyltransferase homolog (*S. cerevisiae*)	0.033	0.235
342	55937	APOM	apolipoprotein M	0.022	0.321
343	54206	ERRFI1	ERB8 receptor feedback inhibitor 1	0.016	−1.044
344	283131	NEAT1	nuclear paraspeckle assembly transcript 1 (non-protein coding)	<0.001	−0.528
345	5202	PFDN2	prefoldin subunit 2	0.04	−0.285
346	123	PLIN2	perilipin 2	0.016	0.43
347	81689	ISCA1	iron-sulfur cluster assembly 1 homolog (*S. cerevisiae*)	0.034	0.305
348	6129	RPL7	ribosomal protein L7	0.047	−0.2
349	79370	BCL2L14	BCL2-like 14 (apoptosis facilitator)	0.042	0.25
350	7052	TGM2	transglutaminase 2 (C polypeptide, protein-glutamine-gamma-glutamyltransferase)	0.038	−0.264
351	2332	FMR1	fragile X mental retardation 1	0.002	0.518
352	23066	CAND2	cullin-associated and neddylation-dissociated 2 (putative)	0.031	−0.404
353	4085	MAD2L1	MAD2 mitotic arrest deficient-like 1 (yeast)	0.009	−0.348
354	161	AP2A2	adaptor-related protein complex 2, alpha 2 subunit	0.032	0.374
355	5265	SERPINA1	serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 1	0.041	−0.219
356	388401	RPL7P48	ribosomal protein L7 pseudogene 48	0.016	−0.513
357	51764	GNG13	guanine nucleotide binding protein (G protein), gamma 13	0.047	0.451
358	6720	SREBF1	sterol regulatory element binding transcription factor 1	0.015	0.424
359	610	HCN2	hyperpolarization activated cyclic nucleotide-gated potassium channel 2	0.017	0.262
360	5721	PSME2	proteasome (prosome, macropain) activator subunit 2 (PA28 beta)	0.005	0.774
361	55140	ELP3	elongation protein 3 homolog (*S. cerevisiae*)	0.002	0.596
362	55754	TMEM30A	transmembrane protein 30A	0.023	−0.304
363	1938	EEF2	eukaryotic translation elongation factor 2	0.045	−0.253
364	3843	IPO5	importin 5	0.023	−0.315
365	55967	NDUFA12	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 12	0.039	−0.409
366	51136	RNFT1	ring finger protein, transmembrane 1	0.018	0.351
367	95	ACY1	aminoacylase 1	0.032	0.223
368	3312	HSPA8	heat shock 70 kDa protein 8	0.007	0.277
369	768211	RELL1	RELT-like 1	0.025	−0.304
370	492	ATP2B3	ATPase, Ca++ transporting, plasma membrane 3	0.042	0.251
371	5507	PPP1R3C	protein phosphatase 1, regulatory (inhibitor) subunit 3C	0.022	0.445
372	11189	CELF3	CUGBP, Elav-like family member 3	0.007	0.42

TABLE 3-continued

445 genes differentially expressed in MSC non-exposed in comparison with cells exposed to TCM from sample 1 in comparison with non-exposed cells. The magnitude of the expression change is represented as the logarithm of the fold change.

	GeneID	Name	Description	PValue	Log2FC
373	55177	FAM82A2	family with sequence similarity 82, member 62	0.028	0.382
374	64773	EAM113A	family with sequence similarity 113, member A	0.046	−0.234
375	23612	PHLDA3	pleckstrin homology-like domain, family A, member 3	0.032	0.292
376	9704	DHX34	DEAH (Asp-Glu-Ala-His) box polypeptide 34	0.018	0.26
377	10189	THOC4	THO complex 4	0.005	0.74
378	80196	RNF34	ring finger protein 34	0.029	0.302
379	1303	COL12A1	collagen, type XII, alpha 1	0.013	−0.605
380	26872	STEAP1	six transmembrane epithelial antigen of the prostate 1	0.01	−0.821
381	23645	PPP1R15A	protein phosphatase 1, regulatory (inhibitor) subunit 15A	0.003	0.778
382	3320	HSP90AA1	heat shock protein 90 kDa alpha (cytosolic), class A member 1	0.019	0.418
383	23543	RBFOX2	RNA binding protein, fox-1 homolog (*C. elegans*) 2	0.026	−0.234
384	4540	ND5	NADH dehydrogenase, subunit 5 (complex I)	0.025	−0.228
385	3329	HSPD1	heat shock 60 kDa protein 1 (chaperonin)	0.003	0.472
386	3336	HSPE1	heat shock 30 kDa protein 1 (chaperonin 10)	0.002	0.419
387	2192	FBLN1	fibulin 1	0.009	−0.301
388	55450	CAMK2N1	calcium/calmodulin-dependent protein kinase II inhibitor 1	0.019	0.274
389	80036	TRPM3	transient receptor potential cation channel, subfamily M, member 3	0.012	0.35
390	6330	SCN4B	sodium channel, voltage-gated, type IV, beta	0.045	0.379
391	151300	LOC151300	hypothetical LOC151300	0.028	0.32
392	81614	NIPA2	non imprinted in Prader-Willi/Angelman syndrome 2	0.043	−0.242
393	63910	SLC17A9	solute carrier family 17, member 9	0.015	0.376
394	51386	EIF3L	eukaryotic translation initiation factor 3, subunit L	0.025	−0.252
395	2346	FOLH1	folate hydrolase (prostate-specific membrane antigen) 1	0.013	−0.338
396	3491	CYR61	cysteine-rich, angiogenic inducer, 61	<0.001	−0.829
397	2730	GCLM	glutamate-cysteine ligase, modifier subunit	<0.001	0.508
398	10957	PNRC1	proline-rich nuclear receptor coactivator 1	0.041	0.215
399	25805	BAMBI	BMP and activin membrane-bound inhibitor homolog (*Xenopus laevis*)	0.034	0.315
400	1831	TSC22D3	TSC22 domain family, member 3	0.019	0.349
401	3161	HMMR	hyaluronan-mediated motility receptor (RHAMM)	0.041	0.27
402	81567	TXNDC5	thioredoxin domain containing 5 (endoplasmic reticulum)	0.026	−0.324
403	5955	RCN2	reticulocalbin 2, EF-hand calcium binding domain	0.001	−0.414
404	3920	LAMP2	lysosomal-associated membrane protein 2	0.017	−0.223
405	254128	LOC254128	hypothetical LOC254128	0.019	0.284
406	51734	SEPX1	selenoprotein X, 1	0.027	0.241
407	10105	PPIF	peptidylprolyl isomerase F	0.003	0.455
408	284630	LOC284630	hypothetical protein LOC284630	0.038	−0.355
409	51187	RSL24D1	ribosomal L24 domain containing 1	0.026	−0.439
410	8227	AKAP17A	A kinase (PRKA) anchor protein 17A	0.018	0.376
411	29081	METTL5	methyltransferase like 5	0.009	−0.516
412	10379	IRF9	interferon regulatory factor 9	<0.001	0.427
413	4071	TMSF1	transmembrane 4 L six family member 1	0.01	−0.337
414	83667	SESN2	sestrin 2	0.003	0.491
415	1649	DDIT3	DNA-damage-inducible transcript 3	<0.001	1.17
416	5708	PSMD2	proteasome (prosome, macropain) 26S subunit, non-ATPase, 2	0.015	−0.289
417	223082	ZNRF2	zinc and ring finger 2	0.018	0.389
418	64778	FNDC3B	fibronectin type III domain containing 38	0.028	−0.339
419	388533	KRTDAP	keratinocyte differentiation-associated protein	0.027	−0.258
420	3646	EIF3E	eukaryotic translation initiation factor 3, subunit E	0.036	−0.277
421	56917	MEIS3	Meis homeobox 3	0.033	0.274
422	10410	IFITM3	interferon induced transmembrane protein 3 (1-8U)	0.017	0.243
423	55970	GNG12	guanine nucleotide binding protein (G protein), gamma 12	0.04	−0.31
424	7474	WNT5A	wingless-type MMTV integration site family, member 5A	0.04	−0.489
425	84231	TRAF2	TNF receptor-associated factor 7	0.039	−0.429
426	329	BIRC2	baculoviral IAP repeat containing 2	0.043	−0.352
427	9518	GDF15	growth differentiation factor 15	<0.001	0.604
428	83606	C22orf13	chromosome 22 open reading frame 13	0.049	−0.411
429	3337	DNAJB1	DnaJ (Hsp40) homolog, subfamily B, member 1	<0.001	0.945
430	389223	EEF1A1P35	eukaryotic translation elongation factor 1 alpha 1 pseudogene 35	0.027	−0.218
431	26118	WSB1	WD repeat and SOCS box containing 1	<0.001	−0.583
432	79368	FCRL2	Fc receptor-like 2	0.01	−0.388
433	1809	DPYSL3	dihydropyrimidinase-like 3	0.043	−0.235
434	2744	GLS	glutaminase	0.016	−0.348
435	4735	SEPT2	septin 2	0.022	−0.38
436	79670	ZCCHC6	zinc finger, CCHC domain containing 6	0.044	0.222
437	29115	SAP30BP	SAP30 binding protein	0.011	0.259
438	5252	PHF1	PHD finger protein 1	0.042	0.275
439	3312	HSPA8	heat shock 70 kDa protein 8	0.004	0.369
440	3725	JUN	jun proto-oncogene	0.014	0.36
441	3638	INSIG1	insulin induced gene 1	0.02	0.333
442	146225	CMTM2	CKLF-like MARVEL transmembrane domain containing 2	0.049	0.289
443	5440	POLR2K	polymerase (RNA) II (DNA directed) polypeptide K, 7.0 kDa	0.03	−0.288

TABLE 3-continued

445 genes differentially expressed in MSC non-exposed in comparison with cells exposed to TCM from sample 1 in comparison with non-exposed cells. The magnitude of the expression change is represented as the logarithm of the fold change.

	GeneID	Name	Description	PValue	Log2FC
444	157317	CYCSP55	cytochrome c, somatic pseudogene 5S	0.01	0.35
445	6520	SLC3A2	solute carrier family 3 (activators of dibasic and neutral amino acid transport), member 2	0.005	0.468

TABLE 4

511 genes differentially expressed in MSC non-exposed in comparison with cells exposed to TCM from sample 2 in comparison with non-exposed cells. The magnitude of the expression change is represented as the logarithm of the fold change.

	GeneID	Name	Description	PValue	Log2FC
1	54769	DIRAS2	DIRAS family, GTP-binding RAS-like 2	0.024	0.445
2	1958	EGR1	early growth response 1	0.002	−0.727
3	56109	PCDHGA6	protocadherin gamma subfamily A, 6	0.041	−0.303
4	11137	PWP1	PWP1 homolog (*S. cerevisiae*)	0.01	−0.356
5	92609	TIMM50	translocase of inner mitochondrial membrane 50 homolog (*S. cerevisiae*)	0.045	0.341
6	1968	EIF2S3	eukaryotic translation initiation factor 2, subunit 3 gamma, 52 kDa	0.02	−0.443
7	1719	DHFR	dihydrofolate reductase	0.03	0.325
8	1728	NQO1	NAD(P)H dehydrogenase, quinone 1	0.03	−0.639
9	85445	CNTNAP4	contactin associated protein-like 4	0.006	0.445
10	6782	HSPA13	heat shock protein 70 kDa family, member 13	0.011	−0.57
11	81626	SHC8P1L	SHC SH2 domain binding protein 1-like	<0.001	0.751
12	2959	GTF2B	general transcription factor IIB	0.041	0.462
13	51278	IER5	immediate early response 5	<0.001	0.774
14	8028	MLLT10	myeloid/lymphoid or mixed-lineage leukemia (trithorax homolog, *Drosophila*) translocated to, 10	0.039	0.516
15	1282	COL4A1	collagen, type IV, alpha 1	0.019	−0.377
16	2199	FBLN2	fibulin 2	<0.001	0.676
17	3438	IGF8P5	insulin-like growth factor binding proten 5	<0.001	0.602
18	57104	PNPLA2	patatin-like phospholipase domain containing 2	0.033	0.956
19	10659	CELF2	CUGBP, Elav-like family member 2	<0.001	1.078
20	635	BHMT	betaine-homocysteine S-methyltransferase	0.042	0.414
21	50613	UBQLN3	ubiquilin 3	0.011	0.417
22	56950	SMYD2	SET and MYND domain containing 2	0.009	0.835
23	56097	PCDHGC5	protocadherin gamma subfamily C, 5	0.042	−0.408
24	6396	SEC13	SEC13 homolog (*S. cerevisiae*)	0.048	−0.318
25	51310	SLC22A17	solute carrier family 22, member 17	0.004	0.362
26	10945	KDELR1	KDEL (Lys-Asp-Glu-Leu) endoplasmic reticulum protein retention receptor 1	0.033	−0.342
27	10938	EHD1	EH-domain containing 1	0.002	0.61
28	79370	BCL2L14	BCL2-like 14 (apoptosis facilitator)	0.027	0.387
29	2657	GDF1	growth differentiation factor 1	0.014	0.407
30	3954	LETM1	leucine zipper-EF-hand containng transmembrane protein 1	0.003	−0.407
31	7278	TUBA3C	tubulin, alpha 3c	<0.001	0.507
32	2574	GAGE2C	G antigen 2C	0.002	0.522
33	10476	ATP5H	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit d	0.029	−0.352
34	7323	UBE2D3	ubiquitin-conjugating enzyme E2D 3 (UBC4/5 homolog, yeast)	0.014	0.35
35	8404	SPARCL1	SPARC-like 1 (hevin)	0.007	0.592
36	55062	WIPI1	WD repeat domain, phosphoinositide interacting 1	<0.001	−0.696
37	29116	MYLIP	myosin regulatory light chain interacting protein	<0.001	0.871
38	55907	CMAS	cytidine monophosphate N-acetyineuraminic acid synthetase	0.033	0.346
39	55000	TUG1	taurine upregulated 1 (non-protein coding)	0.004	0.59
40	1672	DEFB1	defensin, beta 1	<0.001	0.721
41	11145	PLA2G16	phospholipase A2, group XVI	0.005	0.402
42	10814	CPLX2	complexin 2	0.004	0.458
43	2191	FAP	fibroblast activation protein, alpha	<0.001	−0.59
44	1634	DCN	decorin	0.004	−0.311
45	114804	RNF157	ring finger protein 157	0.031	0.385
46	972	CD74	CD74 molecule, major histocompatibility complex, class II invariant chain	0.042	0.344
47	26137	2BTB20	zinc finger and BTB domain containing 20	0.003	0.536
48	10524	KATS	K(lysine) acetyltransferase S	0.043	−0.329
49	266655	NCRNA00094	non-protein coding RNA 94	0.043	−0.307
50	100271071	RPS17P10	ribosomal protein S17 pseudogene 10	0.025	−0.513
51	56970	ATXN7L3	ataxin 7-like 3	0.013	−0.418
52	7117	TMSL3	thymosin-like 3	0.022	−0.322
53	9789	SPCS2	signal peptidase complex subunit 2 homolog (*S. cerevisiae*)	0.038	0.334
54	2969	GTF2I	general transcription factor III	0.02	0.37

TABLE 4-continued

511 genes differentially expressed in MSC non-exposed in comparison with cells exposed to TCM from sample 2 in comparison with non-exposed cells. The magnitude of the expression change is represented as the logarithm of the fold change.

	GeneID	Name	Description	PValue	Log2FC
55	6129	RPL7	ribosomal protein L7	0.02	−0.304
56	388692	LOC388692	hypothetical LOC388692	0.019	0.404
57	9524	TECR	trans-2,3-enoyl-CoA reductase	0.038	0.42
58	79630	C1orf54	chromosome 1 open reading frame 54	0.032	−0.481
59	5138	PDE2A	phosphodiesterase 2A cGMP-stimulated	0.022	0.61
60	283131	NEAT1	nuclear paraspeckle assembly transcript 1 (non-protein coding)	0.038	−0.471
61	8943	AP3D1	adaptor-related protein complex 3, delta 1 subunit	0.007	0.309
62	467	ATF3	activating transcription factor 3	<0.001	1.187
63	54996	MOSC2	MOCO sulphurase C-terminal domain containing 2	0.004	0.736
64	54600	UGT1A9	UDP glucuronosyltransferase 1 family, polypeptide A9	<0.001	0.686
65	23450	SF3B3	splicing factor 3b, subunit 3, 130 kDa	0.044	0.503
66	221035	REEP3	receptor accessory protein 3	0.04	0.336
67	22907	DHX30	DEAH (Asp-Glu-Ala-His) box polypeptide 30	0.005	−0.339
68	1345	COX6C	cytochrome c oxidase subunit VIc	0.002	0.375
69	219402	MTIF3	mitochondrial translational initiation factor 3	0.013	0.315
70	200185	KRTCAP2	keratinocyte associated protein 2	<0.001	−0.617
71	118945	CTSL1P1	cathepsin L1 pseudogene 1	0.019	−0.467
72	58515	SELK	selenoprotein K	0.006	0.324
73	23095	KIF18	kinesin family member 1B	0.004	0.474
74	9861	PSMD6	proteasome (prosome, macropain) 26S subunit, non-ATPase, 6	0.012	0.366
75	10808	HSPH1	heat shock 105 kDa/110 kDa protein 1	<0.001	0.761
76	9988	DMTF1	cyclin D binding myb-like transcription factor 1	0.015	0.389
77	56110	PCDHGA5	protocadherin gamma subfamily A, 5	0.011	−0.368
78	1387	CREBBP	CREB binding protein	0.033	0.406
79	25907	TMEM158	transmembrane protein 158 (gene/pseudogene)	0.026	−0.494
80	1003	CDH5	cadherin 5, type 2 (vascular endothelium)	0.03	0.518
81	9531	BAG3	BCL2-associated athanogene 3	<0.001	0.78
82	79696	FAM164C	family with sequence similarity 164, member C	0.017	0.465
83	23761	PISD	phosphatidylserine decarboxylase	0.006	0.388
84	2824	GPM6B	glycoprotein M68	0.004	0.429
85	51726	DNAJB11	DnaJ (Hsp40) homolog, subfamily B, member 11	<0.001	0.495
86	478	ATP1A3	ATPase, Na+/K+ transporting, alpha 3 polypeptide	0.003	0.692
87	338799	LOC338799	hypothetical LOC338799	0.016	−0.375
88	9261	MAPKAPK2	mitogen-activaied protein kinase-activated protein kinase 2	0.019	0.408
89	5476	CTSA	cathepsin A	0.004	−0.381
90	533	ATP6V08	ATPase, H+ transporting, lysosomal 21 kDa, V0 subunit b	0.009	0.438
91	6125	RPL5	ribosomal protein E5	0.001	−0.527
92	3336	HSPE1	heat shock 10 kDa protein 1 (chaperonin 10)	0.004	0.509
93	80279	CDK5RAP3	CDK5 regulatory subunit associated protein 3	0.002	0.474
94	441533	RPL26P37	ribosomal protein 126 pseudogene 37	0.003	−0.442
95	6141	RPL18	ribosomal protein L18	0.044	−0.305
96	55964	sep-03	septin 3	0.003	0.54
97	5707	PSMD1	proteasome (prosome, macropain) 26S subunit, non-ATPase, 1	0.036	0.314
98	2353	FOS	FBJ murine osteosarcoma viral oncogene homolog	0.003	0.482
99	55228	PNMAL1	PNMA-like 1	0.011	0.569
100	11215	AKAP11	A kinase (PRKA) anchor protein 11	1.017	0.443
101	57222	ERGIC1	endoplasmic reticulum-golgi intermediate compartment (ERGIC) 1	0.04	−0.314
102	8566	PDXK	pyridoxal (pyridoxine, vitamin B6) kinase	0.002	0.486
103	3703	STT3A	STT3, subunit of the oligosaccharyltransferase complex homolog A (*S. cerevisiae*)	0.004	−0.415
104	4884	NPTX1	neuronal pentraxin I	<0.001	0.762
105	7485	WRB	tryotophan rich basic protein	0.016	0.403
106	11179	ZNF277	zinc finger protein 277	0.004	−0.744
107	3397	ID1	inhibitor of DNA binding 1, dominant negative helix-loop-helix protein	0.001	0.402
108	1611	DAP	death-associated protein	0.042	−0.445
109	53826	FXYD6	FXYD domain containing ion transport regulator 6	<0.001	0.546
110	11170	FAM107A	family with sequence similarity 107, member A	<0.001	0.405
111	66501	SOLH	small optic lobes homolog (*Drosophila*)	0.046	−0.381
112	8985	PLOD3	procollagen-lysine, 2-oxoglutarate 5-dioxygenase 3	0.007	−0.555
113	2496	FTH1P1	ferritin, heavy polypeptide 1 pseudogene	0.006	−0.353
114	3972	LHB	luteinizing hormone beta polypeptide	0.025	−0.31
115	1164	CKS2	CDC28 protein kinase regulatory subunit 2	<0.001	0.712
116	6152	RPL24	ribosomal protein L24	0.006	−0.31
117	145767	RPS3AP6	ribosomal protein S3A pseudogene 6	0.004	−0.361
118	150221	RIMBP3C	RIMS binding protein 3C	0.003	0.388
119	6733	SRPK2	SRSF protein kinase 2	0.008	−0.362
120	23621	BACE1	beta-site APP-cleaving enzyme 1	0.028	−0.307
121	1964	EIF1AX	eukaryotic translation initiation factor 1A, X-linked	0.012	−0.488
122	2983	GUCY1B3	guanylate cyclase 1, soluble, beta 3	<0.001	0.663
123	7546	ZIC2	Zic family member 2 (odd-paired homolog, *Drosophila*)	0.002	0.75
124	51617	HMP19	HMP19 protein	0.003	0.517
125	54476	RNF216	ring finger protein 216	0.004	0.434
126	54657	UGT1A4	UDP glucuronosyltransferase 1 family, polypeptide A4	0.003	0.508

TABLE 4-continued

511 genes differentially expressed in MSC non-exposed in comparison with cells exposed to TCM from sample 2 in comparison with non-exposed cells. The magnitude of the expression change is represented as the logarithm of the fold change.

	GeneID	Name	Description	PValue	Log2FC
127	23786	BCL2L13	BCL2-like 13 (apoptosis facilitator)	<0.001	0.926
128	387103	CENPW	centromere protein W	0.018	0.544
129	5420	PODXL	podocalyxin-like	0.003	0.574
130	23209	MLC1	megalencephalic leukoencephalopathy with subcortical cysts 1	0.005	0.582
131	84303	CHCHD6	coiled-coil-helix-coiled-coil-helix domain containing 6	0.037	0.395
132	392358	RPS6P13	ribosomal protein S6 pseudogene 13	0.006	−0.319
133	3032	HADHB	hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase (trifunctional protein), beta subunit	0.005	−0.355
134	3301	DNAJA1	DnaJ (Hsp40) homolog, subfamily A, member 1	0.002	0.441
135	3047	HBG1	hemoglobin, gamma A	0.023	0.306
136	112714	TUBA3E	tubulin, alpha 3e	0.011	0.301
137	283971	CLEC18C	C-type lectin domain family 18, member C	<0.001	0.588
138	4783	NFIL3	nuclear factor, interleukin 3 regulated	0.013	−0.408
139	6678	SPARC	secreted protein, acidic, cysteine-rich (osteonectin)	0.008	−0.416
140	813	CALU	calumenin	0.042	−0.377
141	116151	C20orf108	chromosome 20 open reading frame 108	0.013	−0.641
142	57730	ANKRD36B	ankyrin repeat domain 368	0.018	0.336
143	6154	RPL26	ribosomal protein L26	0.031	−0.307
144	51386	EIF3L	eukaryotic translation initiation factor 3, subunit L	0.034	−0.32
145	7175	TPR	translocated promoter region (to activated MET oncogene)	0.009	0.489
146	54504	CPVL	carboxypeptidase, vitellogenic-like	0.003	0.442
147	7058	THBS2	thrombosporidin 2	0.025	−0.328
148	9452	ITM2A	integral membrane protein 2A	0.009	0.621
149	2131	EXT1	exostosin 1	0.009	−0.426
150	65055	REEP1	receptor accessory protein 1	0.033	0.308
151	79791	FBXO31	F-box protein 31	0.005	0.42
152	3936	LCP1	lymphocyte cytosolic protein 1 (L-plastin)	0.029	0.528
153	90701	SEC11C	SEC11 homolog C (*S. cerevisiae*)	0.002	0.569
154	84681	HINT2	histidine triad nucleotide binding protein 2	0.02	0.354
155	26749	GAGE2E	G antigen 2E	0.039	0.312
156	7644	ZNF91	zinc finger protein 91	0.034	0.335
157	231	AKR1B1	aldo-keno reductase family 1, member 81 (aldose reductase)	<0.001	−0.543
158	91942	NDUFAF2	NADH dehvdrogenase (ubiquinone) 1 alpha subcomplex, assembly factor 2	0.032	0.419
159	501	ALDH7A1	aldehyde dehydrogenase 7 family, member A1	0.008	−0.422
160	26099	C1orf144	chromosome 1 open reading frame 144	0.036	0.333
161	4131	MAP1B	microtubule-associated protein 1B	<0.001	0.724
162	84545	MRPL43	mitochondrial ribosomal protein L43	0.007	−0.515
163	4358	MPV17	MpV17 mitochondrial inner membrane protein	0.017	−0.345
164	51031	GLOD4	glyoxalase domain containing 4	0.029	0.407
165	22928	SEPH52	selenophosphate synthetase 2	0.003	0.413
166	60312	AFAP1	actin filament associated protein 1	<0.001	−0.632
167	291	SLC25A4	solute carrier family 25 (mitochondrial carrier adenine nucleotide translocator), member 4	0.019	0.313
168	26608	TBL2	transducin (beta)-like 2	0.02	0.391
169	55753	OGDHL	oxoglutarate dehydrogenase-like	0.01	0.37
170	8468	FK8P6	FKS06 binding protein 6, 36 kDa	0.002	0.418
171	10472	ZNF238	zinc finger protein 238	0.034	0.384
172	1164	CKS2	CDC28 protein kinase regulatory subunit 2	<0.001	0.345
173	132864	CPEB2	cytoplasmic polyadenylation element binding protein	<0.001	0.475
174	55731	C17orf63	chromosome 17 open reading frame 63	0.016	0.341
175	54752	FNDC8	fibronectin type III domain containing 8	0.011	−0.373
176	89958	C9orf140	chromosome 9 open reading frame 140	0.041	−0.328
177	220594	LOC220594	ubiquitin specific peptidase 6 (Tre-2 oncogene) pseudogene	0.044	0.32
178	51616	TAF9B	TAF9B RNA polymerase II, TATA box binding protein (TBP)-associated factor, 31 kDa	0.049	0.325
179	5297	PI4KA	phosphatidylinositol 4-kinase, catalytic, alpha	0.017	0.332
180	8802	SUCLG1	succinate-CoA ligase, alpha subunit	<0.001	0.594
181	6601	SMARCC2	SWI/SNF related, matrix associated, actin dependent regulator of chromatin subfamily c, member 2	0.033	−0.854
182	81688	C6orf62	chromosome 6 open reading framed	<0.001	0.413
183	54658	UGT1A1	UDP glucuronosyltransferase 1 family, polypeptide A1	0.013	0.336
184	79753	SNIP1	Smad nuclear interacting protein 1	<0.001	0.364
185	65009	NDRG4	NDRG family member 4	<0.00	0.452
186	51596	CUTA	cutA divalent cation tolerance homolog (*E. coli*)	0.005	−0.363
187	2938	GSTA1	glutathione S-transferase alpha 1	0.025	0.367
188	3337	DNAJB1	DnaJ (Hsp40) homolog, subfamily B, member 1	<0.001	0.581
189	6189	RPS3A	ribosomal protein S3A	0.024	−0.313
190	113457	TUBA3D	tubulin, alpha 3d	0.028	0.673
191	2171	FABP5	fatty acid binding protein 5 (psoriasis-associated)	0.006	0.374
192	2619	GAS1	growth arrest-specific 1	0.001	−0.481
193	7980	TFP12	tissue factor pathway inhibitor 2	0.001	−0.97
194	51655	RASD1	RAS, dexamethasone-induced 1	<0.001	−0.827
195	1293	COL6A3	collagen, type VI, alpha 3	0.032	−0.342

TABLE 4-continued

511 genes differentially expressed in MSC non-exposed in comparison with cells exposed to TCM from sample 2 in comparison with non-exposed cells. The magnitude of the expression change is represented as the logarithm of the fold change.

	GeneID	Name	Description	PValue	Log2FC
196	83955	NACAP1	nascent-polypeptide-associated complex alpha polypeptide pseudogene 1	0.009	−0.447
197	9444	QKI	quaking homolog, KH domain RNA binding (mouse)	0.01	0.553
198	387763	C11orf96	chromosome 11 open reading frame 96	0.001	0.447
199	128218	TMEM125	transmembrane protein 125	0.03	0.419
200	7873	MANF	mesencephalic astrocyte-derived neurotrophic factor	0.003	0.44
201	64750	SMURF2	SMAD specific E3 ubiquitin protein ligase 2	<0.001	−0.495
202	3476	IGBP1	immunoglobulin (CD79A) binding protein 1	<0.001	−0.551
203	400963	RPS2P17	ribosomal protein S2 pseudogene 17	0.008	−0.346
204	79925	SPEF2	sperm flagellar 2	0.014	0.38
205	9736	KIAA0S86	KIAA0S86	0.031	0.349
206	25874	BRP44	brain protein 44	0.018	0.722
207	55964	sep-03	septin 3	0.019	0.579
208	84935	C13orf33	chromosome 13 open reading frame 33	0.011	−0.35
209	10370	CITED2	Cbp/p300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain, 2	0.013	−0.429
210	55693	KDM4D	lysine (K)-specific demethylase 4D	0.046	0.483
211	1490	CTGF	connective tissue growth factor	0.004	−0.456
212	89781	HPS4	Hermansky-Pudlak syndrome 4	0.004	0.6
213	9547	CXCL14	chemokine (C-X-C motif) ligand 14	<0.001	0.831
214	121549	ASCL4	achaete-scute complex homolog 4 (*Drosophila*)	0.028	0.324
215	7415	VCP	valosin containing protein	0.007	0.368
216	29118	DDX25	DEAD (Asp-Glu-Ala-Asp) box polypeptide 25	0.009	0.645
217	100271475	RPL31P51	ribosomal protein L31 pseudogene 51	0.035	−0.31
218	55695	NSUNU	NOP2/Sun domain family, member 5	0.01	0.315
219	5937	RBMS1	RNA binding motif, single stranded interacting protein 1	<0.001	−0.521
220	127933	UHMK1	U2AF homology motif (UHM) kinase 1	0.015	−0.301
221	8553	8HLHE40	basic helix-loop-helix family, member e40	<0.001	0.905
222	54659	UGT1A3	UDP glucuronosyltransferase 1 family, polypeptide A3	0.026	0.704
223	83639	TEX101	testis expressed 101	0.035	0.378
224	8742	TNFSF12	tumor necrosis factor (ligand) superfamily, member 12	0.01	−0.548
225	5045	FURIN	furin (paired basic amino acid cleaving enzyme)	0.005	0.502
226	267	AMFR	autocrine motility factor receptor	0.022	−0.324
227	390158	RPLSP29	ribosomal protein LS pseudogene 29	0.002	−0.477
228	2939	GSTA2	glutathione S-transferase alpha 2	0.007	0.474
229	29968	PSAT1	phosphoserine aminotransferase 1	0.007	0.476
230	151579	BZW1P2	basic leucine zipper and W2 domains 1 pseudogene 2	0.004	−0.344
231	115207	KCTD12	potassium channel tetramerisation domain containing 12	<0.001	−0.807
232	26353	HSP88	heat shock 22 kDa protein 8	0.038	0.461
233	283711	LOC283711	ubiquitin-conjugating enzyme E2C pseudogene	0.017	0.388
234	3225	HOXC9	homeobox C9	0.031	0.371
235	4553	TRNA	tRNA	<0.001	1.002
236	255313	CT47A11	cancer/testis antigen family 47, member A11	0.014	0.368
237	55002	TMCO3	transmembrane and coiled-coil domains 3	0.003	−0.366
238	79143	MBOAT7	membrane bound O-acyltransferase domain containing 7	0.019	−0.321
239	9547	CXCL14	chemokine (C-X-C motif) ligand 14	0.025	0.392
240	130827	TMEM182	transmembrane protein 182	0.011	0.434
241	3322	HSP90AA3P	heat shock protein 90 kDa alpha (cytosolic), class A member 3 (pseudogene)	<0.001	0.764
242	345645	LOC345645	proteasome (prosome, macropain) 26S subunit, ATPase, 1 pseudogene	0.023	0.346
243	5539	PPY	pancreatic polypeptide	0.008	1.063
244	5934	RBL2	retinoblastoma-like 2 (p130)	0.02	−0.388
245	1743	DLST	dihydrolipoamide S-succinyltransferase (E2 component of oxo-glutarate complex)	0.006	0.37
246	10054	UBA2	ubiquitin-like modifier activating enzyme 2	0.013	0.407
247	7196	TRNAG2	transfer RNA glycine 2 (anticodon GCC)	0.013	0.693
248	114569	MAL2	mal, T-cell differentiation protein 2 (gene/pseudogene)	0.049	0.342
249	8491	MAP4K3	mitogen-activated protein kinase kinase kinase kinase 3	0.025	0.32
250	4609	MYC	v-myc myelocytomatosis viral oncogene homolog (avian)	0.029	0.369
251	28970	C11orf54	chromosome 11 open reading frame 54	0.035	0.321
252	1462	VCAN	versican	0.013	0.419
253	51191	HERC5	hect domain and RLD 5	0.006	0.44
254	92591	ASB16	ankyrin repeat and SOCS box containing 16	0.007	0.407
255	341032	C11orf53	chromosome 11 open reading frame 53	0.046	−0.405
256	6446	SGK1	serum/glucocorticoid regulated kinase 1	0.04	0.36
257	9082	XKRY	XK, Kell blood group complex subunit-related, Y-linked	0.003	0.433
258	349114	NCRNA00265	non-protein coding RNA 265	0.002	0.512
259	3304	HSPA1B	heat shock 70 kDa protein 1B	<0.001	0.919
260	122953	JDP2	Jun dimerization protein 2	0.007	0.447
261	84791	C1orf97	chromosome 1 open reading frame 97	0.001	0.478
262	4649	MYO9A	myosin IXA	0.008	0.351
263	91012	LASS5	LAG1 homolog, ceramide synthase 5	0.009	−0.42
264	4070	TACSTD2	tumor-associated calcium signal transducer 2	0.04	0.319

TABLE 4-continued

511 genes differentially expressed in MSC non-exposed in comparison with cells exposed to TCM from sample 2 in comparison with non-exposed cells. The magnitude of the expression change is represented as the logarithm of the fold change.

	GeneID	Name	Description	PValue	Log2FC
265	63908	NAPB	N-ethylmaleimide-sensitive factor attachment protein, beta	0.013	0.328
266	144110	TMEM86A	transmembrane protein 86A	0.027	0.348
267	51659	GINS2	GINS complex subunit 2 (Psf2 homolog)	0.018	0.321
268	51009	DERL2	Derl-like domain family, member 2	0.003	0.334
269	5936	RBM4	RNA binding motif protein 4	0.031	0.336
270	4353	MPO	myeloperoxidase	0.048	0.327
271	23014	FBXO21	F-box protein 21	0.018	−0.359
272	283711	LOC283711	ubiquitin-conjugating enzyme E2C pseudogene	0.035	0.35
273	376497	SLC27A1	solute carrier family 27 (fatty acid transporter), member 1	0.012	−0.372
274	7381	UQCRB	ubiquinol-cytochrome c reductase binding protein	0.038	0.346
275	6888	TALDO1	transaldolase 1	0.008	−0.436
276	9052	GPRC5A	G protein-coupled receptor, family C, group 5, member A	0.008	0.313
277	23394	ADNP	activity-dependent neuroprotector homeobox	0.01	0.419
278	6303	SAT1	spermidine/spermine N1-acetyltransferase 1	0.001	−0.444
279	390638	LOC390638	Golgin subfamily A member 2-like	0.041	−0.356
280	339799	EIF3FP3	eukaryotic translation initiation factor 3, subunit F pseudogene 3	0.008	−0.357
281	55138	FAM90A1	family with sequence similarity 90, member A1	0.023	0.33
282	5721	PSME2	proteasome (prosome, macropain) activator subunit 2 (PA28 beta)	0.007	0.328
283	26262	TSPAN17	tetraspanin 17	0.012	−0.411
284	1827	RCAN1	regulator of calcineurin 1	<0.001	−0.991
285	8660	IRS2	insulin receptor substrate 2	0.018	0.339
286	8490	RGS5	regulator of G-protein signaling 5	0.044	0.393
287	3043	HBB	hemoglobin, beta	0.009	0.519
288	9099	USP2	ubiquitin specific peptidase 2	0.029	0.373
289	388815	C21orf34	chromosome 21 open reading frame 34	0.035	0.308
290	3434	IFIT1	interferon-induced protein with tetratricopeptide repeats 1	<0.001	0.426
291	51019	CCDC53	coiled-coil domain containing 53	0.014	0.37
292	116832	RPL39L	riposomal protein L39-like	0.042	0.368
293	389180	S-HT3C2	S-HT3c2 serotonin receptor-like protein pseudogene	0.013	0.341
294	55319	C4orf43	chromosome 4 open reading frame 43	0.014	0.316
295	150160	CCT8L2	chaperonin containing TCP1 subunit 8 (theta)-like 2	0.019	0.335
296	3398	ID2	inhibitor of DNA binding 2, dominant negative helix-loop-helix protein	<0.001	−0.452
297	6166	RPL36AL	ribosomal protein L36a-like	0.008	−0.327
298	284996	RNF149	ring finger protein 149	0.005	0.408
299	283070	LOC283070	hypothetical LOC283070	0.016	0.386
300	7447	VSNL1	visinin-like 1	0.047	0.306
301	151636	DTX3L	deltex 3-like (*Drosophila*)	0.049	0.638
302	1612	DAPK1	death-associated protein kinase 1	0.02	0.493
303	55818	KDM3A	lysine (K)-specific demethylase 3A	0.002	0.451
304	83447	SLC25A31	solute carrier family 25 (mitochondrial carrier, adenine nucleotide translocator), member 31	0.033	0.447
305	9555	H2AFY	H2A histone family member 7	0.031	−0.613
306	10523	CHERP	calcium homeostasis endoplasmic reticulum protein	0.008	0.423
307	51652	VPS24	vacuolar protein sorting 24 homolog (*S. cerevisiae*)	0.011	0.322
308	64215	DNAJC1	DnaJ (Hsp40) homolog, subfamily C, member 1	0.007	−0.457
309	4170	MCL1	myeloid cell leukemia sequence 1 (BCL2-related)	<0.001	0.484
310	3324	HSP90AA2	heat shock protein 90 kDa alpha (cytosolic), class A member 2	<0.001	0.624
311	57092	PCNP	PEST proteolytic signal containing nuclear protein	0.012	−0.355
312	2697	GIA1	gap junction protein, alpha 1, 43 kDa	0.029	−0.335
313	2745	GLRX	glutaredoxin (thioltransferase)	0.013	0.468
314	4048	LTA4H	leukotriene A4 hydrolase	0.026	−0.39
315	6899	TBX1	T-box 1	0.019	−0.359
316	10241	CALCOCO2	calcium binding and coiled-coil domain 2	0.007	0.322
317	260436	C4orf7	chromosome 4 open reading frame 7	0.004	0.504
318	7280	TUBB2A	tubulin, beta 2A	0.001	0.474
319	3930	L8R	lamin 8 receptor	0.042	0.372
320	5638	PRRG1	proline rich Gla (G-carboxyglutamic acid) 1	0.016	−0.389
321	23174	ZCCHC14	zinc finger, CCHC domain containing 14	0.007	0.392
322	399665	FAM102A	family with sequence similarity 102, member A	0.013	0.314
323	10450	PPIE	peptidylprolyl isomerase E (cyclophilin E)	0.005	−0.384
324	26232	FBXO2	F-box protein 2	0.009	−0.378
325	4567	TRNL1	tRNA	0.001	0.527
326	83880	EIF3FP2	eukaryotic translation initiation factor 3, subunit F pseudogene 2	0.024	−0.389
327	51074	APIP	APAF1 interacting protein	0.035	0.383
328	30001	ERO1L	ERO1-like (*S. cerevisiae*)	0.033	0.418
329	115207	KCTD12	potassium channel tetramerisation domain containing 12	0.03	−0.431
330	5159	PDGFRB	platelet-derived growth factor receptor, beta polypeptide	0.029	−0.419
331	23201	FAM168A	family with sequence similarity 168, member A	0.016	0.311
332	339229	C17orf90	chromosome 17 open reading frame 90	0.022	0.336
333	3303	HSPA1A	heat shock 70 kDa protein 1A	<0.001	1.468
334	23024	PDZRN3	PDZ domain containing ring finger 3	0.039	−0.403
335	10628	TXNIP	thioredoxin interacting protein	<0.001	−0.764
336	84272	YIPF4	Yip1 domain family, member 4	0.022	−0.373

TABLE 4-continued

511 genes differentially expressed in MSC non-exposed in comparison with cells exposed to TCM from sample 2 in comparison with non-exposed cells. The magnitude of the expression change is represented as the logarithm of the fold change.

	GeneID	Name	Description	PValue	Log2FC
337	9636	ISG15	ISG15 ubiquitin-like modifier	0.003	0.937
338	391656	RPS1SAPI7	ribosomal protein S1Sa pseudogene 17	0.046	−0.302
339	7207	TRNAL1	transfer RNA leucine 1 (anticodon AAG)	0.003	0.407
340	51454	GULP1	GULP, engulfment adaptor PT8 domain containing 1	0.001	−0.685
341	9709	HERPUD1	homocysteine-inducible, endoplasmic reticulum stress-inducible, ubiquitin-like domain member 1	<0.001	0.719
342	55032	SLC35A5	solute carrier family 35, member A5	0.021	0.503
343	885	CCK	cholecystokinin	0.009	0.569
344	1728	NQO1	NAD(P)H dehydrogenase, quinone 1	0.003	−0.757
345	9445	ITM2B	integral membrane protein 2B	0.021	0.424
346	2	A2M	alpha-2-macroglobulin	0.047	0.571
347	3766	RA811A	RA811A, member RAS oncogene family	0.017	−0.31
348	55251	PCMTD2	protein-L-isoaspartate (D-aspartate) O-methyltransferase domain containing 2	0.011	−0.485
349	6428	SRSF3	serine/arginine- rich splicing factor 3	<0.001	0.575
350	10922	FASTK	Fas-activated serine/threonine kinase	0.021	−0.409
351	433	ASGR2	asialoglycoprotein receptor 2	0.012	0.318
352	9510	ADAMTS1	ADAM metallopeptidase with thrombospondin type 1 motif, 1	0.002	−0.556
353	7754	ZNF204P	zinc finger protein 204, pseudogene	0.014	0.335
354	440275	EIF2AK4	eukaryotic translation initiation factor alpha kinase 4	0.025	−0.796
355	11098	PRSS23	protease, serine, 23	0.027	0.311
356	79174	CRELD2	cysteine-rich with EGF-like domains 2	0.008	0.458
357	25946	ZNF385A	zinc finger protein 385A	0.003	−0.458
358	26053	AUTS2	autism susceptibility candidate 2	0.032	0.46
359	2743	GLRB	glycine receptor, beta	0.013	0.322
360	440073	IQSEC3	IQ motif and Sec7 domain 3	0.008	0.464
361	7180	CRISP2	cysteine-rich secretory protein 2	0.007	0.459
362	2297	FOXD1	forkhead box D1	0.04	0.311
363	9246	UBE2L6	ubiquitin-conjugating enzyme E2L6	0.005	0.391
364	6236	RRAD	Ras-related associated with diabetes	<0.001	0.841
365	7291	TWIST1	twist homolog 1 (*Drosophila*)	0.041	−0.488
366	4982	TNFRSF11B	tumor necrosis factor receptor superfamily, member 11b	0.006	−0.567
367	57212	KIAA0495	KIAA0495	0.038	0.351
368	28999	KLF15	Kruppel-like factor 15	<0.001	0.852
369	3207	HOXA11	homeobox A11	0.02	0.576
370	6938	TCF12	transcription factor 12	0.026	0.422
371	116254	C6orf72	chromosome 6 open reading frame 72	0.003	−0.346
372	51187	RSL24D1	ribosomal L24 domain containing 1	0.012	−0.327
373	7804151	SNORD3A	small nucleolar RNA, C/D box 3A	0.043	0.576
374	731275	LOC731275	hypothetical LOC731275	0.032	−0.339
375	143689	PIWIL4	piwi-like 4 (*Drosophila*)	<0.001	0.592
376	85363	TRIM5	tripartite motif containing 5	0.006	0.366
377	9520	NPEPPS	aminopeptidase puromycin sensitive	0.002	−0.387
378	290	ANPEP	alanyl (membrane) aminopeptidase	0.01	−0.314
379	1317	SLC31A1	solute carrier family 31 (copper transporters), member 1	0.002	0.461
380	55197	RPRD1A	regulation of nuclear pre-mRNA domain containing 1A	0.049	−0.322
381	9670	IPO13	importin 13	0.033	−0.408
382	90850	ZNF598	zinc finger protein 598	0.046	−0.34
383	92258	CCDC645	coiled-coil domain containing 64	0.014	−0.474
384	165215	FAM171B	family with sequence similarity 171, member B	0.038	0.353
385	283131	NEAT1	nuclear paraspeckle assembly transcript 1 (non-protein coding)	0.002	−0.396
386	5202	PFDN2	prefoldin subunit 2	0.005	−0.417
387	57106	NAT14	N-acetyltransferase 14 (GCN5-related, putative)	0.037	−0.399
388	255512	LOC255512	hypothetical LOC255512	0.039	0.442
389	123	PLIN2	perillpin 2	0.018	0.423
390	6389	SDHA	succinate dehydrogenase complex, subunit A, flavoprotein (Fp)	0.037	−0.317
391	2577	GAGES	G antigen 5	0.037	0.31
392	10487	CAP1	CAP, adenylate cyclase-associated protein 1 (yeast)	0.033	−0.369
393	79370	BCL2L14	BCL2-like 14 (apoptosis facilitator)	0.012	0.32
394	2332	FMR1	fragile X mental retardation 1	0.006	0.436
395	56105	PCDHGA11	protocadherin gamma subfamily A, 11	0.014	−0.316
396	3976	LIF	leukemia inhibitory factor (cholinergic differentiation factor)	0.01	−0.469
397	8701	DNAH11	dynein, axonernal, heavy chain 11	0.012	0.363
398	58512	DLGAP3	discs, large (*Drosophila*) homolog-associated protein 3	0.025	0.361
399	51764	GNG13	guanine nucleotide binding protein (G protein), gamma 13	0.043	0.462
400	9043	SPAG9	sperm associated antigen 9	0.032	−0.38
401	8754	ADAM9	ADAM metallopeptidase domain 9	0.037	−0.399
402	57466	SCAF4	SR-related CTD-associated factor 4	0.018	0.32
403	51495	PTPLAD1	protein tyrosine phosohatase-like A domain containing 1	0.011	−0.359
404	8495	PPFIBP2	PTPRF interacting protein, binding protein 2 (liprin beta 2)	0.042	−0.381
405	10777	ARPP21	cAMP-regulated phosphoprotein, 21 kDa	0.01	0.324
406	1938	EEF2	eukaryotic translation elongation factor 2	0.019	−0.305
407	6007	RHD	Rh blood group, D antigen	0.003	0.644
408	4363	ABCC1	ATP-binding cassette, sub-family C (CFTR/MRP), member 1	0.015	−0.441

TABLE 4-continued

511 genes differentially expressed in MSC non-exposed in comparison with cells exposed to TCM from sample 2 in comparison with non-exposed cells. The magnitude of the expression change is represented as the logarithm of the fold change.

	GeneID	Name	Description	PValue	Log2FC
409	26585	GREM1	gremlin 1	0.02	−0.568
410	492	ATP2B3	ATPase, Ca++ transporting, plasma membrane 3	0.006	0.358
411	5507	PPP1R3C	protein phosphatase 1, regulatory (inhibitor) subunit 3C	0.002	0.644
412	51635	DHRS7	dehydrogenase/reductase (SDR family) member 7	0.006	−0.362
413	26025	PCDHGA12	protocadherin gamma subfamily A, 12	0.005	−0.513
414	1808	DPYSL2	dihydropyrimidinase-like 2	0.037	0.355
415	9704	DHX34	DEAH (Asp-Glu-Ala-His) box polyoeptide 34	0.008	0.301
416	80196	RNF34	ring finger protein 34	0.016	0.34
417	26872	STEAP1	six transmembrane epithelial antigen of the prostate 1	0.015	−0.768
418	23645	PPP1R15A	protein phosphatase 1, regulatory (inhibitor) subunit 15A	<0.001	0.923
419	729171	ANKRD20A8P	ankyrin repeat domain 20 family, member A8, pseudogene	0.023	0.351
420	3320	HSP90AA1	heat shock protein 90 kDa alpha (cytosolic), class A member 1	0.006	0.505
421	10539	GLRX3	glutaredoxin 3	0.014	0.388
422	2585	GALK2	galactokinase 2	0.037	−0.31
423	5707	PSMD1	proteasome (prosome, macropain) 26S subunit, non-ATPase, 1	0.043	−0.756
424	2791	GNG11	guanine nucleotide binding protein (G protein), gamma 11	0.005	−0.511
425	3371	TNC	tenascin C	0.015	−0.327
426	5036	PA2G4	proliferation-associated 2G4, 38 kDa	0.005	0.4
427	3329	HSPD1	heat shock 60 kDa protein 1 (chaperonin)	0.009	0.398
428	3336	HSPE1	heat shock 10 kDa protein 1 (chaperonin 10)	0.012	−0.331
429	80036	TRPM3	transient receptor potential cation channel, subfamily M, member 3	0.009	0.368
430	158293	FAM120AOS	family with sequence similarity 120A opposite strand	0.006	0.376
431	6330	SON4B	sodium channel, voltage-gated, type IV, beta	0.028	0.421
432	151300	LOC151300	hypothetical LOC151300	0.018	0.35
433	63910	SLC17A9	solute carrier family 17, member 9	0.007	0.429
434	51386	EIF3L	eukaryotic translation initiation factor 3, subunit L	<0.001	−0.417
435	4728	NDUFS8	NADH dehydrogenase (ubiquinone) Fe-S protein 8, 23 kDa (NADH-coenzyme Q reductase)	0.045	0.307
436	6899	TBX1	T-box 1	0.018	−0.357
437	3491	CYR61	cysteine-rich, angiogenic inducer, 61	<0.001	−0.767
438	2730	GCLM	glutamate-cysteine ligase, modifier subunit	0.002	0.445
439	8438	RAD54L	RAD54-like (*S. cerevisiae*)	0.003	0.398
440	1831	TSC22D3	TSC22 domain family, member 3	0.016	0.359
441	81567	TXNDCS	thioredoxin domain containing S (endoplasmic reticulum)	0.016	−0.357
442	5955	RCN2	reticulocalbin 2, EF-hand calcium binding domain	0.013	−0.302
443	523	ATP6V1A	ATPase, H+ transporting, lysosomal 70 kDa, V1 subunit A	0.028	−0.319
444	254128	LOC254128	hypothetical LOC254128	<0.001	0.442
445	9184	BUB3	budding uninhibited by benzimidazoles 3 hornolog (yeast)	0.032	−0.336
446	9045	RPL14	ribosomal protein L14	0.049	−0.369
447	402207	LOC402207	putative TAF11-like protein ENSP00000332601-like	0.025	0.64
448	27245	AHDC1	AT hook, DNA binding motif, containing 1	0.029	0.378
449	10105	PPIF	peptidylprolyl isomerase F	0.02	0.338
450	4616	GADD45B	growth arrest and DNA-damage-inducible, beta	0.002	0.513
451	29081	METTL5	methyltransferase like 5	0.005	−0.565
452	4071	TM4SF1	transmembrane 4 L six family member 1	0.001	−0.46
453	23339	VPS39	vacuolar protein sorting 39 homolog (*S. cerevisiae*)	0.031	−0.36
454	1649	DDIT3	DNA-damage-inducible transcript 3	<0.001	1.049
455	55701	ARHGEF40	Rho guanine nucleotide exchange factor (GEF) 40	0.015	−0.355
456	10159	ATP6AP2	ATPase, H+ transporting, lysosomal accessory protein 2	0.024	−0.305
457	5708	PSMD2	proteasome (prosome, macropain) 26S subunit, non-ATPase, 2	0.008	−0.319
458	223082	ZNRF2	zinc and ring finger 2	0.03	0.351
459	64778	FNDC38	fibronectin type II domain containing 3B	0.04	−0.314
460	4430	MYO1B	myosin IB	0.032	−0.442
461	11098	PRSS23	protease, serine, 23	0.019	0.302
462	2066	ER884	v-erb-a erythroblastic leukemia viral oncogene homolog 4 (avian)	0.007	0.333
463	9092	SART1	squamous cell carcinoma antigen recognized by T cells	0.019	0.374
464	2339	FNTA	farnesyltransferase, CAAX box, alpha	0.027	−0.301
465	23433	RHOQ	ras homolog gene family, member Q	0.01	0.384
466	5230	PGK1	phosphoglycerate kinase 1	0.04	0.345
467	84231	TRAF7	TNF receptor-associated factor 7	0.026	−0.468
468	9518	GDF15	growth differentiation factor 15	<0.001	0.601
469	23265	EXOC7	exocyst complex component 7	0.03	−0.305
470	4017	LOXL2	lysyl oxidase-like 2	0.034	−0.407
471	7374	UNG	uracil-DNA glycosylase	0.047	−0.313
472	3337	DNAJB1	DnaJ (Hsp40) homolog, subfamily B, member 1	<0.001	0.977
473	729992	ST13P1	suppression of tumorigenicity 13 (colon carcinoma) (Hsp70 interacting protein) pseudogene 1	0.014	−0.345
474	10777	ARPP21	cAMP-regulated phosphoprotein, 21 kDa	0.006	0.353
475	1809	DPYSL3	dihydropyrimidinase-like 3	0.007	−0.33
476	3480	IGF1R	insulin-like growth factor 1 receptor	0.002	−0.893
477	51471	NAT8B	N-acetyltransferase 8B (GCNS-related, putative, gene/pseudogene)	0.04	0.395
478	10550	ARL6IP5	ADP-ribosylation-like factor 6 interacting protein 5	0.023	−0.389
479	57092	PCNP	PEST proteolytic signal containing nuclear protein	0.006	−0.338
480	9276	COPB2	coatomer protein complex, subunit beta 2 (beta prime)	0.01	−0.464

TABLE 4-continued

511 genes differentially expressed in MSC non-exposed in comparison with cells exposed to TCM from sample 2 in comparison with non-exposed cells. The magnitude of the expression change is represented as the logarithm of the fold change.

	GeneID	Name	Description	PValue	Log2FC
481	388394	RPRML	reprimo-like	0.008	−0.447
482	51124	IER3IP1	immediate early response 3 interacting protein 1	0.003	−0.648
483	7763	ZFANDS	zinc finger, AN1-type domain 5	0.019	−0.345
484	11171	STRAP	serine/threonine kinase receptor associated protein	0.01	−0.441
485	2203	FBP1	fructose-1,6-bisphosphatase 1	0.044	−0.474
486	125	ADH1B	alcohol dehydrogenase 1B (class I), beta polypeptide	0.036	−0.68
487	10494	STK75	serine/threonine kinase 25	0.008	−0.367
488	285902	LOC285902	hypothetical LOC285902	0.026	0.454
489	51255	RNF181	ring finger protein 181	0.045	−0.349
490	2787	GNG5	guanine nuceotide binding protein (6 protein), gamma 5	0.031	−0.554
491	6319	SCD	stearoyl-CoA desaturase (delta-9-desaturase)	0.045	0.362
492	442582	STAG3L2	stromal antigen 3-like 2	0.046	−0.361
493	9085	CDY1	chromodomain protein, Y-linked, 1	0.014	0.39
494	6443	SGCB	sarcoglycan, beta (43 kDa dystrophin-associated glycoprotein)	0.028	−0.712
495	6347	CCL2	chemokine (C-C motif) ligand 2	0.02	0.465
496	10289	EIF18	eukaryotic translation initiation factor 1B	0.023	−0.378
497	51699	VPS29	vacuolar protein sorting 29 homolog (*S. cerevisiae*)	0.001	−0.546
498	3725	JUN	jun proto-oncogene	0.027	0.317
499	3476	IG8P1	immunoglobulin (CD79A) binding protein 1	0.023	−0.363
500	2794	GNL1	guanine nucleotide binding protein-like 1	0.006	−0.353
501	9689	BZW1	basic leucine zipper and W2 domains 1	0.047	−0.312
502	5791	PTPRE	protein tyrosine phosphatase, receptor type, E	0.002	−0.388
503	150962	PUS10	pseudouridylate synthase 10	0.007	0.332
504	409	ARRB2	arrestin, beta 2	0.046	−0.388
505	5440	POLR2K	polymerase (RNA) II (DNA directed) polypeptide K, 7.0 kDa	0.005	−0.396
506	9159	PCSK7	proprotein convertase subtilisin/kexin type 7	0.048	−0.401
507	53340	SPA17	sperm autoantigenic protein 17	0.045	−0.328
508	10776	ARPP19	cAMP-regulated phosphoprotein, 19 kDa	0.017	0.474
509	440595	EEF1A1P11	eukaryotic translation elongation factor 1 alpha 1 pseudogene 11	0.002	−0.402
510	157317	CYCSP55	cytochrome c, somatic pseudogene 55	0.023	0.3
511	6520	SLC3A2	solute carrier family 3 (activators of dibasic and neutral amino acid transport), member 2	0.002	0.553

TABLE 5

521 genes differentially expressed in MSC non-exposed in comparison with cells exposed to TCM from sample 4 in comparison with non-exposed cells. The magnitude of the expression change is represented as the logarithm of the fold change.

	GeneID	Name	Description	PValue	Log2FC
1	54769	DIRAS2	DIRAS family, GTP-binding RAS-like 2	0.016	0.483
2	1314	COPA	coatomer protein complex, subunit alpha	0.001	−0.507
3	25912	C1orf43	chromosome 1 open reading frame 43	<0.001	−0.567
4	10625	IVNS1ABP	influenza virus NS1A binding protein	0.036	−0.403
5	23516	SLC39A14	solute carrier family 39 (zinc transporter), member 14	0.001	−0.527
6	11137	PWP1	PWP1 homolog (*S. cerevisiae*)	0.011	−0.35
7	100133941	CD24	CD24 molecule	<0.001	0.757
8	51375	SNX7	sorling nexin 7	0.007	0.748
9	378	ARF4	ADP-ribosylation factor 4	0.006	−0.34
10	302	ANAX2	annexin A2	0.008	0.388
11	85445	CNTNAP4	contactin associated protein-like 4	0.006	0.445
12	5214	PFKP	phosphofructokinase, platelet	0.018	0.372
13	6782	HSPA13	heat shock protein 70 kDa family, member 13	<0.001	−1.416
14	817	CAMK2D	calcium/calmodulin-dependent protein kinase II delta	0.043	−0.369
15	81626	SHCBP1L	SHC SH2-domain binding protein 1-like	<0.001	0.905
16	2959	GTF2B	general transcription factor IIB	0.033	0.487
17	51278	IER5	immediate early response 5	0.008	0.516
18	54541	DDIT4	DNA-damage-inducible transcript 4	<0.001	−0.472
19	2199	FBLN2	fibulin 2	0.015	0.338
20	3488	IGFBP5	insulin-like growth factor binding protein 5	<0.001	0.63
21	57104	PNPLA2	patatin-like phospholipase domain containing 2	0.046	0.887
22	10659	CELF2	CUGBP, Elav-like family member 2	<0.001	0.903
23	635	BHMT	betaine--homocysteine S-methyltransferase	0.004	0.635
24	50613	UBQLN3	uhiquilin 3	0.001	0.57
25	3569	IL6	interleukin 6 (interferon, beta 2)	0.024	−0.515
26	1123	CHN1	chimerin (chimaerin) 1	0.046	0.33
27	6396	SEC13	SEC13 homolog (*S. cerevisiae*)	0.002	−0.557
28	51310	SLC22A17	solute carrier family 22, member 17	0.002	0.396
29	10938	EHD1	EH-domain containing 1	0.01	0.49
30	2657	GDF1	growth differentiation factor 1	0.026	0.362

TABLE 5-continued

521 genes differentially expressed in MSC non-exposed in comparison with cells exposed to TCM from sample 4 in comparison with non-exposed cells. The magnitude of the expression change is represented as the logarithm of the fold change.

	GeneID	Name	Description	PValue	Log2FC
31	51727	CMPK1	cytidine monophosphate (UMP-CMP) kinase 1, cytosolic	0.034	−0.317
32	56951	C5orf15	chromosome 5 open reading frame 15	0.003	0.429
33	3954	LETM1	leucine zipper-EF-hand containing transmembrane protein 1	0.015	−0.323
34	7278	TUBA3C	tubulin, alpha 3c	0.004	0.354
35	2574	GAGE2C	G antigen 2C	<0.001	0.722
36	10476	ATP5H	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit d	0.047	−0.315
37	9588	PRDX6	peroxiredoxin 6	0.049	0.339
38	5756	TWF1	twinfilin, actin-binding protein, homolog 1 (*Drosophila*)	0.041	−0.729
39	3091	HIFlA	hypoxia inducible factor 1, alpha subunit (basic helix-loop-helix transcription factor)	<0.001	−0.808
40	8404	SPARCL1	SPARC-like 1 (hevin)	<0.001	0.82
41	55062	WIPI1	WD repeat domain, phosphoinositide interacting 1	<0.001	−0.729
42	55273	TMEM100	transmembrane protein 100	0.029	0.523
43	29116	MYLIP	myosin regulatory light chain interacting protein	0.003	0.53
44	55907	CMAS	cytidine monophosphate N-acetylneuraminic acid synthetase	0.027	0.36
45	4809	NHP2L1	NHP2 non-histone chromosome protein 2-like 1 (*S. cerevisiae*)	0.017	0.38
46	1672	DEFB1	defensin, beta 1	<0.001	0.679
47	11145	PLA2G16	phospholipase A2, group XVI	0.003	0.436
48	10769	PLK2	polo-like kinase 2	<0.001	0.684
49	10618	TGOLN2	trans-golgi network protein 2	0.03	0.427
50	10814	CPLX2	complexin 2	0.013	0.379
51	2191	FAP	fibroblast activation protein, alpha	0.007	−0.424
52	90507	SCRN2	secernin 2	0.043	0.37
53	386677	KRTAP10-1	keratin associated protein 10-1	0.008	−0.367
54	1912	PHC2	polyhomeotic homolog 2 (*Drosophila*)	0.046	−0.466
55	2969	GTF2I	general transcription factor III	0.041	0.318
56	8894	EIF2S2	eukaryotic translation initiation factor, subunit 2 beta, 38 kDa	0.012	−0.668
57	79630	C1orf54	chromosome 1 open reading frame 54	0.044	−0.448
58	10099	TSPAN3	tetraspanin 3	0.025	0.339
59	3486	IGF8P3	insulin-like growth factor binding protein 3	0.004	0.453
60	8943	AP3D1	adaptor-related protein complex 3, delta 1 subunit	0.006	−0.319
61	467	ATF3	activating transcription factor 3	<0.001	0.801
62	54704	PDP1	pyruvate dehyrogenase phosphatase catalytic subunit 1	0.03	0.384
63	90411	MCFD2	multiple coagulation factor deficiency 2	0.013	−0.414
64	4141	MARS	methionyl-tRNA synthetase	0.004	−0.446
65	54996	MOSC2	MOCO sulphurase C-terminal domain containing 2	0.018	0.583
66	7127	TNFAIP2	tumor necrosis factor, alpha-induced protein	<0.001	1.116
67	54600	UGT1A9	UDP glucuronosyltransferase 1 family, polypeptide A9	0.002	0.523
68	23471	TRAM1	translocation associated membrane protein 1	0.005	−0.513
69	64065	PERP	PERP, TP53 apoptosis effector	0.014	0.413
70	10135	NAMPT	nicotinamide phosphoribosyltransferase	<0.001	−1.102
71	4637	MYL6	myosin, light chain 6, alkali, smooth muscle and non-muscle	0.002	0.338
72	389493	LOC389493	hypothetical protein LOC389493	0.035	0.576
73	3295	HSD17B4	hydroxysteroid (17-beta) dehydrogenase 4	<0.001	−0.726
74	112936	VPS268	vacuolar protein sorting 26 homolog B (*S. pombe*)	0.019	0.527
75	58515	SELK	selenoprotein K	<0.001	−0.514
76	4739	NEDD9	neural precursor cell expressed, developmentally down-regulated 9	0.012	0.495
77	10808	HSPH1	heat shock 105 kDa/110 kDa protein 1	0.011	0.359
78	60685	ZFAND3	zinc finger, AN1-type domain 3	0.005	−0.413
79	64208	POPDC3	popeye domain containing 3	0.044	−0.41
80	3399	ID3	inhibitor of DNA binding 3, dominant negative helix-loop-helix protein	<0.001	0.659
81	8092	ALX1	ALX homeobox 1	0.043	−0.449
82	8480	RAE1	RAE1 RNA export 1 homolog (*S. pombe*)	0.005	0.488
83	813	CALU	calumenin	0.023	−0.407
84	4190	MDH1	malate dehydrogenase 1, NAD (soluble)	0.021	0.308
85	23562	CLDN14	claudin 14	0.006	−0.575
86	7184	HSP90B1	heat shock protein 90 kDa beta (Grp94), member 1	<0.001	−0.603
87	6418	SET	SET nuclear oncogene	0.045	0.316
88	3376	IARS	isoleucyl-tRNA synthetase	<0.001	−0.663
89	92140	MTDH	metadherin	0.002	−0.496
90	8321	F2D1	frizzled homolog 1 (*Drosophila*)	0.006	0.582
91	5270	SERPINE2	serpin peptidase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1), member 2	0.008	−0.373
92	55829	SELS	selenoprotein S	<0.001	−0.604
93	25907	TMEM158	transmembrane protein 158 (gene/pseudogene)	0.004	−0.673
94	1003	CDH5	cadherin 5, type 2 (vascular endothelium)	<0.001	0.969
95	9919	SEC16A	SEC16 homolog A (*S. cerevisiae*)	0.017	−0.325
96	9531	BAG3	BCL2-associated athanogene 3	0.021	0.349
97	79696	FAM164C	family with sequence similarity 164, member C	0.032	0.413
98	2824	GPM6B	glycoprotein M6B	<0.001	0.643
99	478	ATP1A3	ATPase, Na+/K+ transporting, alpha 3 polypeptide	0.034	0.454
100	338799	LOC338799	hypothetical LOC338799	0.025	−0.347
101	9261	MAPKAPK2	mitogen-activated protein kinase-activated protein kinase 2	0.031	0.369
102	158056	MAMDC4	MAM domain containing 4	0.034	−0.366

TABLE 5-continued

521 genes differentially expressed in MSC non-exposed in comparison with cells exposed to TCM from sample 4 in comparison with non-exposed cells. The magnitude of the expression change is represented as the logarithm of the fold change.

	GeneID	Name	Description	PValue	Log2FC
103	5908	RAP1B	RAP1B, member of RAS oncogene family	0.014	−0.315
104	3313	HSPA9	heat shock 70 kDa protein 9 (mortalin)	<0.001	−0.595
105	2578	GAGE6	G antigen 6	0.03	0.411
106	3336	HSPE1	heat shock 10 kDa protein 1 (chaperosin 10)	0.004	0.516
107	441533	RPL26P37	ribosomal protein L26 pseudogene 37	0.022	−0.312
108	10987	COPS5	COP constitutive photomorphogenic homolog subunit 5 (*Arabidopsis*)	0.041	0.337
109	23648	SSBP3	single stranded DNA binding protein 3	0.038	−0.308
110	55964	SEPT3	septin 3	0.008	0.475
111	2353	FOS	FBJ murine osteosarcoma viral oncogene homolog	0.004	0.464
112	55228	PNMAL1	PNMA-like 1	0.001	0.764
113	3306	HSPA2	heat shock 70 kDa protein 2	0.007	0.49
114	57222	ERGIC1	endoplasmic reticulum-golgi intermediate compartment (ERGIC) 1	0.033	−0.328
115	51727	CMPK1	cytidine monophosphate (UMP-CMP) kinase 1, cytosolic	0.035	−0.383
116	8566	PDXK	pyridoxal (pyridoxine, vitamin B6) kinase	0.007	0.397
117	3703	STT3A	STT3, subunit of the oligosaccharyltransferase complex, homolog A (*S. cerevisiae*)	<0.001	−0.54
118	55182	RNF220	ring finger protein 220	0.047	0.465
119	4884	NPTX1	neuronal pentraxin I	0.001	0.697
120	7485	WRB	tryptophan rich basic protein	0.021	0.38
121	3397	ID1	inhibitor of DNA binding 1, dominant negative helix-loop-helix protein	0.006	0.317
122	1611	DAP	death-associated protein	0.046	−0.436
123	391165	RPS26P17	ribosomal protein S26 pseudogene 17	0.02	0.351
124	79039	DDX54	DEAD (Asp-Glu-Ala-Asp) box polypepticle 54	0.018	−0.316
125	8985	PLOD3	procollagen-lysine, 2-oxoglutarate 5-dioxygenase 3	0.028	−0.432
126	28964	GIT1	G protein-coupled receptor kinase interacting ArfGAP 1	<0.001	−0.516
127	2496	FTH1P1	ferritin, heavy polypeptide 1 pseudogene	0.01	−0.326
128	1164	CKS2	CDC28 protein kinase regulatory subunit	<0.001	0.638
129	8662	EIF38	eukaryotic translation initiation factor 3, subunit B	0.014	−0.378
130	51014	TMED7	transmembrane emp24 protein transport domain containing 7	0.013	−0.374
131	1513	CTSK	cathepsin K	0.013	0.387
132	7546	ZIC2	Zic family member (odd-paired homolog, *Drosophila*)	0.044	0.433
133	1266	CNN3	calponin 3, acidic	<0.001	0.432
134	81552	VOPP1	vesicular, overexpressed in cancer, prosurvival protein 1	0.033	0.314
135	23209	MLC1	megalencephalic leukoencephalopathy with subcortical cysts 1	0.019	0.465
136	6472	SHMT2	serine hydroxymethyltransferase 2 (mitochondrial)	0.017	−0.46
137	51081	MRPS7	mitochondrial ribosomal protein 57	0.002	0.36
138	665	BNIP3L	BCL2/adenovirus E1B 19 kDa interacting protein 3-like	0.004	−0.398
139	3032	HADH8	hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thialase/enoyl-CoA hydratase (trifunctional protein), beta subunit	0.003	−0.38
140	4493	MT1E	metallothionein 1E	0.049	−0.322
141	3301	DNAJA1	DnaJ (Hsp40) homolog, subfamily A, member 1	<0.001	0.654
142	9315	C5orf13	chromosome 5 open reading frame 13	<0.001	0.51
143	7102	TSPAN7	tetraspanin 7	0.034	0.411
144	4783	NFIL3	nuclear factor, interleukin 3 regulated	0.03	−0.348
145	81669	CCNL2	cyclin L2	0.005	−0.361
146	81892	C14orf156	chromosome 14 open reading frame 156	0.006	−0.354
147	813	CALU	calumenin	0.001	−0.656
148	23352	UBR4	ubiquitin protein ligase E3 component n-recognin 4	0.002	−0.44
149	113246	C12orf57	chromosome 12 open reading frame 57	0.04	−0.313
150	2697	GJA1	gap junction protein, alpha 1, 43 kDa	0.023	−0.469
151	10439	OLFM1	olfactomedin 1	0.027	0.39
152	83692	CD99L2	CD99 molecule 0.008	0.323	
153	7175	TPR	translocated promoter region (to activated MET oncogene)	0.008	0.495
154	25840	METIL7A	methyltransferase like 7A	0.036	0.413
155	26528	DAZAP1	DAZ associated protein 1	0.02	0.413
156	10484	SEC23A	Sec23 homolog A (*S. cerevisiae*)	0.045	−0.312
157	7058	THBS2	thrombospondin 2	0.008	−0.399
158	9452	ITM2A	integral membrane protein 2A	0.002	0.769
159	65055	REEP1	receptor accessory protein 1	<0.001	0.604
160	9581	PREPL	prolyl endopeptidase-like	0.028	0.711
161	79791	FBXO31	F-box protein 31	0.013	0.367
162	3936	LCP1	lymphocyte cytosolic protein 1 (L- lastin)	<0.001	0.89
163	9536	PTGES	prostaglandin E synthase	0.012	−0.623
164	83657	DYNLRB2	dynein, light chain, roadblock-type 2	0.02	0.357
165	6892	TAPBP	TAP binding protein (tapasin)	0.005	0.379
166	10797	MTFIED2	methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 2, methenyltetrahydrofolate cyclohydrolase	0.004	−0.401
167	26749	GAGE2E	G antigen 2E	0.016	0.373
168	231	AKR181	aldo-keto reductase family 1, member 81 (aldose reductase)	<0.001	−0.473
169	6175	RPLP0	ribosomal protein, large, P0	0.003	−0.319
170	501	ALDH7A1	aldehyde dehydrogenase 7 family, member A1	0.028	−0.335
171	4358	MPV17	MpV17 mitochondrial inner membrane protein	0.02	−0.336
172	54881	TEX10	testis expressed 10	0.011	−0.39
173	60312	AFAP1	actin fiiament associated protein 1	0.023	−0.381

TABLE 5-continued

521 genes differentially expressed in MSC non-exposed in comparison with cells exposed to TCM from sample 4 in comparison with non-exposed cells. The magnitude of the expression change is represented as the logarithm of the fold change.

	GeneID	Name	Description	PValue	Log2FC
174	291	SLC25A4	solute carrier family 25 (mitochondrial carrier adenine nucleotide translocator), member 4	0.012	0.339
175	10472	ZNF238	zinc finger protein 238	0.049	0.353
176	1164	CKS2	CDC28 protein kinase regulatory subunit 2	<0.001	0.394
177	4710	NDUF134	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4 15 kDa	0.018	−0.363
178	653639	LYPLA2P1	lysophospholipase II pseuclogene 1	0.033	−0.376
179	51616	TAF9B	TAF9B RNA polymerase II, TATA box binding protein (TBP)-associated factor, 31 kDa	0.026	0.374
180	55829	SELS	selenoprotein S	0.004	−0.394
181	8802	SUCLG1	succinate-CoA ligase, alpha subunit	0.017	0.365
182	196	AHR	aryl hydrocarbon receptor	0.042	−0.367
183	11100	HNRNPLU1	heterogeneous nuclear ribonucleoprotein U-like 1	0.006	−0.33
184	7184	HSP90B1	heat shock protein 90 kDa beta (Grp94), member 1	0.009	−0.321
185	51693	TRAPPC2L	trafficking protein particle complex 2-like	0.008	−0.467
186	7930	TFPI2	tissue factor pathway inhibitor 2	<0.001	−1.357
187	25	ABL1	c-abi oncogene 1, non receptor tyrosine kinase	0.004	−0.351
188	51655	RASD1	RAS, dexamethasone-induced 1	0.001	−0.513
189	821	CANX	calnexin	<0.001	−0.664
190	27288	RBMXL2	RNA binding motif protein, X-linked-like 2	0.03	0.424
191	83955	NACAP1	nascent-polypeptide-associated complex alpha polypeptide pseudogene 1	0.01	−0.445
192	9689	BZW1	basic leucine zipper and W2 domains 1	<0.001	−0.587
193	6387	CXCL12	chemokine (C-X-C motif) ligand 12	0.008	0.399
194	11031	RAB31	RAB31, member RAS oncogene family	0.046	−0.331
195	7873	MANF	mesencephalic astrocyte-derived neurotrophic factor	<0.001	−0.658
196	3476	IGBP1	immunoglobulin (CD79A) binding protein 1	0.005	−0.395
197	5791	PTPRE	protein tyrosine phosphatase, receptor type, E	0.001	−0.458
198	9690	U8E3C	ubiquitin protein ligase E3C	0.002	−0.512
199	84935	C13orf33	chromosome 13 open reading frame 33	0.008	−0.367
200	6734	SRPR	signal recognition particle receptor (docking protein)	<0.001	−0.534
201	445	ASS1	argininosuccinate synthase 1	0.028	−0.402
202	3312	HSPA8	heat shock 70 kDa protein 8	0.001	0.394
203	8553	BHLHE40	basic helix-icop-helix family, member e40	0.003	0.404
204	79770	TXNDC15	thioredoxin domain containing 15	0.018	−0.373
205	84525	HOPX	HOP homeobox	0.015	0.505
206	10079	ATP9A	ATPase, class II, type 9A	0.015	−0.337
207	267	AMFR	autocrine motility factor receptor	<0.001	−0.543
208	694	BTG1	B-cell translocation gene 1, anti-proliferative	0.004	−0.329
209	6281	S100A10	S100 calcium binding protein A10	0.005	0.357
210	2939	GSTA2	glutathione S-transferase alpha 2	0.01	0.452
211	151579	BZW1P2	basic leucine zipper and W2 domains 1 pseudogene 2	<0.001	−0.59
212	51669	TMEM66	transmembrane protein 66	<0.001	−0.42
213	56113	PCDHGA2	protocadherin gamma subfamily A, 2	0.048	−0.305
214	150372	NFAM1	NFAT activating protein with ITAM motif 1	0.011	−0.302
215	442454	LOC442454	ubiqunol-cytochrome c reductase binding protein pseudogene	0.047	−0.346
216	8894	EIF2S2	eukaryotic translation initiation factor , subunit 2 beta. 38 kDa	<0.001	−0.447
217	4553	TRNA	tRNA	0.005	0.499
218	283820	NOMO2	NODAL modulator 2	0.003	−0.323
219	858	CAV2	caveolin 2	0.001	0.493
220	55002	TMCO3	transmembrane and coiled-coil domains 3	<0.001	−0.459
221	4179	CD46	CD46 molecule, complement regulatory protein	0.007	−0.421
222	29015	SLC43A3	solute carrier family 43 member 3	0.014	−0.442
223	2058	EPRS	glutamyl-prolyl-tRNA synthetase	0.006	−0.485
224	10237	SLC35B1	solute carrier family 35, member B1	0.004	−0.468
225	10113	PREB	prolactin regulatory element binding	<0.001	−0.521
226	58986	TMEM8A	transmembrane protein 8A	0.03	−0.43
227	10730	YME1L1	YME1-like 1 (*S. cerevisiae*)	0.01	−0.451
228	27044	SND1	staphylococcal nuclease and tudor domain containing 1	0.009	−0.476
229	83548	COG3	component of oligomeric golgi complex 3	0.023	−0.387
230	5539	PPY	pancreatic polypeptide	0.043	0.766
231	1979	EIF4EBP2	eukaryotic translation initiation factor 4E binding protein 2	0.046	0.367
232	7196	TRNAG2	transfer RNA glycine 2 (anticodon GCC	0.021	−0.638
233	23384	SPECC1L	sperm antigen with calponin homology and coiled-coil domains 1-like	0.025	−0.364
234	2581	GALC	galactosylceramidase	0.029	−0.548
235	4311	MME	membrane metailo-endopeptidase	0.006	−0.358
236	857	CAV1	caveolin 1, caveolae protein, 22 kDa	0.001	0.394
237	84961	FBXL20	F-box and leucine-rich repeat protein 20	0.009	−0.492
238	10130	PDIA6	protein disulfide isomerase family A, member 6	<0.001	−0.533
239	1462	VCAN	versican	0.028	0.364
240	2926	GRSF1	G-rich RNA sequence binding factor 1	0.002	−0.383
241	84270	C9orf89	chromosome 9 open reading frame 89	<0.001	−0.493
242	341032	C11orf53	chromosome 11 open reading frame 53	0.033	−0.436
243	4191	MDH2	malate dehydrogenase 2, NAD (mitochondrial)	0.004	−0.308
244	7979	SHFM1	split hand/foot malformation (ectrodactyly) type 1	0.03	0.37
245	51458	RHCG	Rh family, C glycoprotein	0.012	0.369

TABLE 5-continued

521 genes differentially expressed in MSC non-exposed in comparison with cells exposed to TCM from sample 4 in comparison with non-exposed cells. The magnitude of the expression change is represented as the logarithm of the fold change.

	GeneID	Name	Description	PValue	Log2FC
246	441198	LOC441198	similar to Heat shock cogntate 71 kDa protein	0.01	0.351
247	29982	NRBF2	nuclear receptor binding factor	0.001	−0.361
248	23546	SYNGR4	synaptogyrin 4	0.028	0.352
249	3304	HSPA1B	heat shock 70 kDa protein B	0.001	0.505
250	57580	PREX1	phosphatidylinositol-3,4,5-trisphosphate-dependent Rac exchange factor 1	0.022	−0.401
251	56005	C19orf10	chromosome 19 open reading frame 10	0.006	−0.356
252	9326	ZNHIT3	zinc finger, HIT-type containing 3	0.03	−0.304
253	65980	BRD9	bromodomain containing 9	0.002	−0.51
254	58515	SELK	selenoprotein K	<0.001	−0.785
255	84866	TMEM25	transmembrane protein 25	0.005	−0.386
256	51009	DERL2	Der-like domain family, member 2	<0.001	−0.603
257	5886	RAD23A	RAD23 homolog A (*S. cerevisiae*)	0.038	−0.332
258	304	ANXA2P2	annexin A2 pseudogene 2	0.023	0.313
259	253832	ZDHHC20	zinc finger, DHHC-type containing 20	0.003	−0.511
260	376267	RAB15	RAB15, member RAS onocogene family	0.02	−0.425
261	79139	DERL1	Der1-like domain family, member 1	0.004	−0.534
262	376497	SLC27A1	solute carrier family 27 (fatty acid transporter), member 1	0.019	−0.343
263	58472	SQRDL	sulfide quinone reductase-like (yeast)	0.028	−0.376
264	9810	RNF40	ring finger protein 40	0.044	−0.3
265	10959	TMED2	transmembrane emp24 domain trafficking protein 2	0.002	−0.434
266	200316	APOBEC3F	apolipoprotein B mRNA editing enzyme, catalytic poiypeptide-like 3F	0.046	−0.36
267	1645	AKR1C1	aldo-keto reductase family 1, member C1 (dihydrodiol dehydrogenase 1; 20-alpha (3-alpha)-hydroxysteroid dehydrogenase)	0.006	−0.579
268	10383	TUBB2C	tubulin beta 2C	<0.001	0.421
269	S1030	FAM1881	family with sequence similarity 18, member 81	<0.003	−0.56
270	29781	NCAPH2	non-SMC condensin II complex, subunit H2	0.012	−0.511
271	1153	CIRBP	cold inducible RNA binding protein	0.02	−0.306
272	6303	SAT1	spermidine/spermine N1-acetyltransferase 1	<0.001	−0.615
273	10620	ARID3B	AT rich interactive domain 3B (BRIGHT-like)	0.025	−1.399
274	22936	ELL2	elongation factor, RNA polymerase II, 2	0.003	−0.372
275	26262	TSPAN17	tetraspanin 17	0.032	−0.34
276	149428	BNIPL	BCL2/adenovirus E1B 19kD interacting protein like	0.027	0.33
277	5111	PCNA	proliferating cell nuclear antigen	0.028	0.43
278	1827	RCAN1	regulator of calcineurin 1	<0.001	−0.555
279	92140	MTDH	metadherin	0.005	−0.412
280	56674	TMEM9B	TMEM9 domain family, member 8	0.034	0.325
281	5916	RARG	retinoic acid receptor, gamma	0.046	−0.425
282	51569	UFM1	ubiquitin-fold modifier 1	0.002	−0.763
283	400	ARL1	ADP-ribosylation factor-like 1	0.032	−0.5
284	10952	SEC61B	Sec61 beta subunit	0.002	−0.416
285	729148	NUS1P1	nuclear undecaprenyl pyrophosphate synthase 1 homolog (*S. cerevisiae*) pseudogene 1	0.011	−0.451
286	9315	C5orf13	chromosome 5 open reading frame 13	0.002	0.388
287	130535	KCTD18	potassium channel tetramerisation domain containing 18	0.039	−0.354
288	5611	DNAJC3	DnaJ (Hsp40) homolog, subfamily C, member 3	<0.001	−1.192
289	54808	DYM	dymeclin	0.003	−0.34
290	51652	VPS24	vacuolar protein sorting 24 homolog (*S. cerevisiae*)	0.007	0.345
291	9527	GOSR1	golgi SNAP receptor complex member 1	0.013	−0.45
292	64215	DNAJC1	DnaJ (Hsp40) homolog, subfamily C, member 1	<0.001	−0.626
293	4170	MCL1	myeloid cell leukemia sequence 1 (BCL2-related)	<0.001	0.46
294	29927	SEC61A1	Sec61 alpha 1 subunit (*S. cerevisiae*)	<0.001	−0.686
295	10123	ARL4C	ADP-ribosylation factor-like 4C	0.004	0.417
296	516	ATPSG1	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit C1 (subunit 9)	0.009	−0.414
297	337973	KRTAP19-6	keratin associated protein 19-6	0.039	−0.304
298	3324	HSP90AA2	heat shock proten 90 kDa alpha (cytosolic), class A member	0.001	0.432
299	57092	PCNP	PEST proteolytic signal containing nuciear protein	0.019	−0.329
300	339122	RAB43	RAB43, member RAS oncogene family	0.003	−0.623
301	54538	ROBO4	roundabout homolog 4, magic roundabout (*Drosophila*)	0.028	0.388
302	7280	TUBB2A	tubulin, beta 2A	<0.001	0.566
303	5168	ENPP2	ectonucleotide pyrophosphatase/phosphodiesterase 2	0.006	0.409
304	1116	CHI3L3	chitinase 3-like1 (cartliage glycoprotein-39)	0.015	−0.315
305	4256	MGP	matrix Gla protein	0.021	0.325
306	81621	KAZALD1	Kazal-type serine peptidase inhibitor domain 1	0.035	−0.388
307	3930	LBR	lamin B receptor	0.026	0.414
308	5638	PRRG1	proline rich Gla (G-carboxyglutamic acid) 1	<0.001	−0.638
309	27309	ZNF330	zinc finger protein 330	0.044	0.488
310	23451	SF3B1	splicing factor 3b, subunit 1, 155 kDa	0.006	−0.32
311	5684	PSMA3	proteasome (prosome, macropain) subunit, alpha type, 3	0.003	−0.337
312	8537	BCAS1	breast carcinoma amplified sequence 1	0.017	0.329
313	133619	PRRC1	proline-rich coiled-coil 1	0.05	−0.306
314	57570	TRMT5	TRM5 tRNA methyltransferase 5 homolog (*S. cerevisiae*)	0.003	0.357
315	1073	CFL2	cofilin 2 (muscle)	0.019	−0.344

TABLE 5-continued

521 genes differentially expressed in MSC non-exposed in comparison with cells exposed to TCM from sample 4 in comparison with non-exposed cells. The magnitude of the expression change is represented as the logarithm of the fold change.

	GeneID	Name	Description	PValue	Log2FC
316	115207	KCTD12	potassium channel tetramerisation domain containing 12	0.048	0.389
317	8577	TMEFF1	transmembrane protein with EGF-like and two follistatin-like domains 1	0.019	−0.395
318	57798	GATAD1	GATA zinc finger domain containing 1	0.023	−0.304
319	201595	STT3B	STT3, subunit of the oligosaccharyltransferase complex, homolog B (*S. cerevisiae*)	0.022	−0.367
320	3303	HSPA1A	heat shock 70 kDa protein 1A	0.002	0.652
321	27332	ZNF638	zinc finger protein 638	0.045	−0.392
322	4314	MMP3	matrix metallopeptidase 3 (stromelysin 1, progelatinase)	0.035	−0.398
323	84272	YIPF4	Yip1 domain family, member 4	0.001	−0.583
324	65108	MARCKSL1	MARCKS-like 1	0.01	0.346
325	284257	BOD1P	biorientation of chromosomes in cell division 1 pseudogene	0.027	0.37
326	51454	GULP1	GULP, engulfment adaptor PTB domain containing 1	0.002	−0.647
327	949	SCARB1	scavenger receptor class B, member 1	0.004	−0.361
328	9709	HERPUD1	homocystaine-inducible, endoplasmic reticulum stress-inducible, ubiquitin-like domain member 1	<0.001	−0.48
329	2195	FAT1	FAT tumor suppressor homolog 1 (*Drosophila*)	0.011	0.423
330	135138	PACRG	PARK2 co-regulated	0.045	0.412
331	10980	COPS6	COP9 constitutive photomorphogenic homolog subunit 6 (*Arabidopsis*)	0.043	−0.343
332	81502	HM13	histocompatibility (minor) 13	<0.001	−0.383
333	85302	FBF1	Fas (TNFRSF6) binding factor 1	0.011	0.31
334	55329	SELS	selenoprotein S	0.01	−0.456
335	55154	MSTO1	misato homolog 1 (*Drosophila*)	0.01	−0.387
336	29058	C20orf30	chromosome 20 open reading frame 30	0.007	−0.357
337	6428	SRSF3	serine/arginine-rich splicing factor 3	0.001	0.397
338	55920	RCC2	regulator of chromosome condensation 2	0.011	0.318
339	92086	GGTLC1	gamma-glutamyltransferase light chain 1	0.008	−0.338
340	3295	HSD17B4	hydroxysteroid (17-beta) dehydrogenase 4	0.004	−0.635
341	23256	SCFD1	sec1 family domain containing 1	0.008	−0.392
342	5479	PPIB	peptidylprolyl isomerase B (cyclophilin 8)	<0.001	−0.61
343	79174	CRELD2	cysteine-rich with EGF-like domains 2	<0.001	−0.928
344	124685	LOC124685	hCG1644301	0.026	0.322
345	S1043	ZBTB7B	zinc finger and BTB domain containing 7B	0.02	−0.311
346	2576	GAGE4	G antigen 4	0.012	0.419
347	6917	TCEA1	transcription elongation factor A (SII), 1	0.016	−0.52
348	202459	OSTCL	oligosaccharyltransferase complex subunit-like	0.035	−0.449
349	51075	TMX2	thioredoxin- related transmembrane protein 2	0.008	−0.452
350	3685	ITGAV	integrin, alpha V (vitronectin receptor, alpha polypeptide, antigen CD51)	0.022	−0.411
351	7358	UGDH	UDP-glucose 6-dehydrogenase	0.037	−0.327
352	7180	CRISP2	cysteine-rich secretory protein 2	0.004	0.502
353	372	ARCN1	archain 1	<0.001	−0.45
354	283902	HTA	hypothetical LOC283902	<0.001	−0.633
355	2035	EPB41	erythrocyte membrane protein band 4.1 (elliptocytosis 1, RH-linked)	0.026	−0.324
356	9246	UBE2L6	ubiquitin-conjugating enzyme E2L 6	0.003	0.424
357	6236	RRAD	Ras-related associated with diabetes	<0.003.	0.625
358	6876	TAGLN	transgelin	0.015	0.482
359	84522	JAGN1	jagunal homolog 1 (*Drosophila*)	0.012	−0.36
360	2938	GSTA1	glutathione S-transferase alpha 1	0.001	0.413
361	92305	TMEM129	transmembrane protein 129	0.017	−0.369
362	2475	MTOR	mechanistic target of rapamycin (serine/threonine kinase)	0.011	−0.352
363	57110	HRASLS	HRAS-like suppressor	0.013	0.4
364	2802	GOLGA3	golgin A3	0.028	−0.339
365	6711	SPTBN1	spectrin, beta, non-erythrocytic 1	0.034	0.393
366	51187	RSL24D1	ribosomal L24 domain containing 1	<0.001	−0.501
367	10952	SEC61B	Sec61 beta subunit	0.009	−0.348
368	10730	YME1L1	YME1-like 1 (*S. cerevisiae*)	0.011	−0.352
369	3459	IFNGR1	interferon gamma receptor 1	0.005	−0.421
370	9520	NPEPPS	aminopeptidase puromycin sensitive	0.012	−0.302
371	290	ANPEP	alanyl (membrane) aminopeptidase	0.005	−0.348
372	246243	RNASEH1	ribonuclease H1	0.004	−0.355
373	2919	CXCL1	chemokine (C-X-C motif) ligand 1 (melanoma growth stimulating activity, alpha)	0.019	0.516
374	29880	ALG5	asparagine-linked glycosylation 5, dolichyl-phosphate beta-glucosyltransferase homolog (*S. cerevisiae*)	0.006	−0.315
375	5935	RBM3	RNA binding motif (RNP1, RRM) protein 3	0.005	0.354
376	55197	RPRD1A	regulation of nuclear pre-mRNA domain containing 1A	0.001	−0.587
377	11260	XPOT	exportin, tRNA (nuclear export receptor for tRNAs)	0.01	−0.454
378	27244	SESN1	sestrin 1	0.001	0.443
379	6382	SDC1	syndecan 1	0.025	0.301
380	283131	NEAT1	nuclear paraspeckle assembly transcript 1 (non-protein coding)	<0.001	−0.607
381	5202	PFDN2	prefoldin subunit 2	0.001	−0.505
382	4490	MT18	metallothionein 18	0.011	−0.47
383	1363	CPE	carboxypeptidase E	0.012	0.36
384	2498	FTH1P3	ferritin, heavy polypeptide 1 pseudogene 3	0.012	−0.361
385	123	PLIN2	perillipin 2	0.003	−0.563

TABLE 5-continued

521 genes differentially expressed in MSC non-exposed in comparison with cells exposed to TCM from sample 4 in comparison with non-exposed cells. The magnitude of the expression change is represented as the logarithm of the fold change.

	GeneID	Name	Description	PValue	Log2FC
386	100287551	LOC100287551	heat shock 70 kDa protein 8 pseudogene	0.009	0.316
387	2577	GAGES	G antigen 5	0.003	0.473
388	2919	CXCL1	chemokine (C-X-C, motif) ligand 1 (melanoma growth stimulating activity, alpha)	0.006	−0.981
389	6767	ST13	suppression of tumorigenicity 13 (colon carcinoma) (Hsp70 interacting protein)	0.031	−0.356
390	6372	CXCL6	chemokine (C-X-C motif) ligand 6 (granulocyte chemotactic protein 2)	0.044	−0.434
391	56311	ANKRD7	ankyrin repeat domain 7	0.049	0.344
392	57561	ARRDC3	arrestin domain containing 3	0.025	0.425
393	2332	FMR1	fragile X mental retardation 1	0.018	0.362
394	7298	TYMS	thymidyiate synthetase	0.003	0.388
395	9792	SERTAD2	SERTA domain containing 2	0.045	−0.363
396	5376	PMP22	peripheral myelin protein 22	0.003	0.432
397	5232	PGK2	phosphoglycerate kinase 2	0.015	0.498
398	5477	SIAH1	seven in absentia homolog 1 (*Drosophila*)	0.046	−0.318
399	8870	IER3	immediate early response 3	0.033	−0.307
400	3976	LIF	leukemia inhibitory factor (cholinergic differentiation factor)	<0.001	−0.681
401	5631	PRPS1	phosphoribosyl pyrophosphate synthetase 1	0.029	0.445
402	51663	ZFR	zinc finger RNA binding protein	0.003	−0.417
403	11260	XPOT	exportin, tRNA (nuclear export receptor for tRNAs)	0.037	−0.436
404	147166	TRIM16L	tripartite motif containing 16-like	0.048	−0.311
405	55140	ELP3	elongation protein 3 homolog (*S. cerevisiae*)	0.001	0.627
406	6387	CXCL12	chemokine (C-X-C motif) ligand 12	0.003	0.478
407	57216	VANGL2	vang-like 2 (van gogh, *Drosophila*)	0.049	−0.39
408	8864	PER2	period homolog 2 (*Drosophila*)	0.046	−0.389
409	54963	UCKL1	uridine-cytidine kinase 1-like 1	0.033	−0.361
410	9695	EDEM1	ER degradation enhancer, mannosidase alpha -like 1	<0.001	−0.67
411	1807	DPYS	dihydropyrimidinase	0.019	0.314
412	3988	LIPA	lipase A, lysosomal acid, cholesterol esterase	0.02	0.347
413	3843	IPO5	importin 5	<0.001	−0.801
414	10440	TIMM17A	translocase of inner mitochondrial membrane 17 homolog A (yeast)	<0.001	−0.633
415	2923	PDIA3	protein disulfide isomerase family A, member 3	0.008	−0.405
416	768211	RELL1	RELT-like 1	0.006	−0.387
417	6432	SRSF7	serine/arginine-rich splicing factor	0.001	0.562
418	55323	LARP6	La ribonucleoprotein domain family, member 6	<0.001	−0.545
419	51635	DHRS7	dehydrogenase/reductase (SDR family) member 7	0.014	−0.318
420	23187	PHLDB1	pleckstrin homology-like domain, family B, member 1	0.016	0.479
421	221458	KIF6	kinesin family member 6	0.045	0.328
422	337967	KRTAP6-2	keratin associated protein 6-2	0.019	0.404
423	665	BNIP3L	BCL2/adenovirus EIB 19 kDa interacting protein 3-like	0.002	−0.464
424	400322	HERC2P2	hect domain and RLD 2 pseudogene 2	0.024	−0.353
425	8528	DDO	D-aspartate oxidase	0.049	0.323
426	26872	STEAP1	six transmembrane epithelial antigen of the prostate 1	0.024	−0.703
427	83853	ROPN1L	rhophilin associated tail protein 1-like	<0.001	0.692
428	51022	GLRX2	glutaredoxin 2	0.005	−0.452
429	2273	FHL1	four and a half LIM domains 1	0.004	0.379
430	729495	FAM108A5P	(putative abhydrolase domain-containing protein FAM108A5	0.004	0.355
431	57149	LYRM1	LYR motif containing 1	0.04	0.365
432	2585	GALK2	galactokinase 2	0.031	−0.322
433	2791	GNG11	guanine nucleotide binding protein (G protein), gamma 11	<0.001	−0.75
434	134492	NUDCD2	NudC domain containing 2	0.022	−0.452
435	23576	DDAH1	dimethylarginine dimethylaminohydrolase 1	0.003	0.413
436	29970	SCHIP1	schwannomin interacting protein 1	0.003	0.445
437	387758	FIBIN	fin bud initiation factor homolog (zebrafish)	0.034	−0.515
438	5156	PDGFRA	platelet-derived growth factor receptor, alpha polypeptide	0.036	−0.443
439	6746	SSR2	signal sequence receptor, beta (translocon -associated protein beta)	0.002	−0.339
440	908	CCT6A	chaperonin containing TCP1, subunit 6A (zeta 1)	0.004	−0.401
441	80204	FBXO11	F-box protein 11	0.001	−0.52
442	25805	BAMBI	BMP and activin membrane-bound inhibitor homolog (*Xenopus laevis*)	0.012	0.387
443	124512	METTL23	methyltransferase like 23	0.015	−0.362
444	1831	TSC22D3	TSC22 domain family, member 3	0.016	0.362
445	54529	ASNSD1	asparagine synthetase domain containing 1	0.02	−0.408
446	6786	STIM1	stromal interaction molecule 1	0.022	−0.312
447	60673	C12orf44	chromosome 12 open reading frame 44	0.002	−0.401
448	170261	ZCCHC12	zinc finger, CCHC domain containing 12	0.002	0.633
449	84076	TKTL2	transketalase-like 2	0.014	0.569
450	10186	LHFP	lipoma HMGIC fusion partner	0.001	0.476
451	4702	NDUFA8	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 8, 19 kDa	0.042	0.301
452	1267	CNP	2',3'-cyclic nucleotide 3' phosphodiesterase	0.011	0.423
453	5535	PPP3R2	protein phosphatase 3, regulatory subunit 8, beta	0.003	0.853
454	10105	PPIF	peptidylprolyl isomerase F	0.013	0.369
455	29993	PACSIN1	protein kinase C and casein kinase substrate in neurons 1	0.015	0.435
456	4616	GADD458	growth arrest and DNA-damage-inducible, beta	<0.001	0.588
457	7364	UGT2B7	UDP glucuronosyltransferase 2 family, polypeptide 87	0.05	0.377

TABLE 5-continued

521 genes differentially expressed in MSC non-exposed in comparison with cells exposed to TCM from sample 4 in comparison with non-exposed cells. The magnitude of the expression change is represented as the logarithm of the fold change.

	GeneID	Name	Description	PValue	Log2FC
458	51187	RSL24D1	ribosomal L24 domain containing 1	0.044	−0.391
459	26748	GAGE12I	G antigen 12I	0.004	0.484
460	55872	PBK	PDZ binding kinase	<0.001	0.68
461	11332	ACOT7	acyl-CoA thioesterase 7	0.002	0.543
462	229	ALDOB	aldolase B, fructose-bisphosphate	0.005	0.413
463	10960	LMAN2	lectin, mannose-binding 2	0.005	−0.319
464	1316	KLF6	Kruppel-like factor 6	<0.001	0.605
465	9915	ARNT2	aryl-hydrocarbon receptor nuclear translocator 2	0.002	0.732
466	1075	CTSC	cathepsin C	0.02	0.423
467	1649	DDIT3	DNA-damage-inducible transcript 3	<0.001	−0.567
468	254778	C8orf46	chromosome 8 open reading frame 46	0.008	0.481
469	146849	CCDC42	coiled-coil domain containing 42	0.01	0.39
470	84951	TNS4	tensin 4	0.012	−0.528
471	223082		zinc and ring finger 2	0.01	0.43
472	64778	FNDC3B	fibronectin type III domain containing 3B	<0.001	−0.586
473	83758	RBP5	retinol binding protein 5, cellular	0.05	0.362
474	4430	MYO1B	myosin 1B	0.021	−0.48
475	11098	PRSS23	protease, serine, 23	<0.001	1.043
476	8547	FCN3	ficolin (collagen/fibrinogen domain containing) 3 (Hakata antigen)	0.046	0.327
477	966	CD59	CD59 molecule, complement regulatory protein	0.002	0.415
478	10841	FTCD	formiminotransferase cyclodeaminase	0.021	−0.41
479	7112	TMPO	thymopoletin	0.015	−0.497
480	8394	PIPSK1A	phosphatidylinositol-4-phosphate 5-kinase, type, alpha	0.028	−0.303
481	10447	FAM3C	family with sequence similarity 3, member C	<0.001	−0.787
482	7474	WNT5A	wingless-type MMTV integration site family, member 5A	0.042	−0.482
483	3948	LDHC	lactate dehydrogenase C	0.016	0.425
484	3337	DNAJB1	DnaJ (Hsp40) homolog, subfamily B, member 1	0.008	0.452
485	7532	YWHAG	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, gamma polypeptide	0.013	0.328
486	4735	SEPT2	septin 2	0.024	−0.374
487	7162	TPBG	trophoblast glycoprotein	0.032	−0.507
488	5354	PLP1	proteolipid protein 1	0.004	0.504
489	59	ACTA2	actin, alpha 2, smooth muscle. aorta	0.008	0.38
490	51471	NAT8B	N-acetyltransferase 8B (GCNS-related, putative, gene/pseudogene)	0.008	0.531
491	10550	ARL6IP5	ADP-ribosylation-like factor 6 interacting protein 5	0.02	−0.401
492	377711	LOC377711	HEAT repeat-containing protein 7A-like	0.006	0.497
493	389453	LOC389493	hypothetical protein LOC389493	0.004	0.416
494	302	ANXA2	annexin A2	0.026	0.326
495	57092	PCNP	PEST proteolytic signal containing nuclear protein	0.013	−0.303
496	2665	GDI2	GDP dissociation inhibitor 2	0.008	−0.349
497	10841	FTCD	formiminotransferase cyclodeaminase	0.008	0.39
498	5992	RFX4	regulatory factor X, 4 (influences HLA class II expression)	0.007	0.534
499	9276	COPB2	coatomer protein complex, subunit beta 2 (beta prime)	0.02	−0.408
500	55352	C17orf79	chromosome 17 open reading frame 79	0.007	0.486
501	2316	FLNA	filamin A, alpha	0.042	0.314
502	54496	PRMT7	protein arginine methyltransferase 7	0.023	−0.307
503	51255	RNF181	ring finger protein 181	0.009	−0.476
504	10135	NAMPT	nicotinamide phosphoribosyltransferase	0.002	−0.741
505	5516	PPP2CB	protein phosphatase 2, catalytic subunit, beta isozyme	0.042	0.302
506	6319	SCD	stearoyl-CoA desaturase (delta-9-desaturase)	0.013	0.468
507	202459	OSTCL	oligosaccharyltransferase complex subunit-like	0.002	−0.611
508	5872	RAB13	RAB13, member RAS oncogene family	0.02	−0.334
509	1645	AKR1C1	aldo-keto reductase family 1, member C1 (dihydrodial dehydrogenase 1; 20-alpha (3-alpha)-hydroxysteroid dehydrogenase)	0.001	−0.543
510	3312	HSPA8	heat shock 70 kDa protein 8	<0.001	0.443
511	477	ATP1A2	ATPase, Na+/K+ transporting, alpha 2 polypeptide	0.009	0.607
512	1277	COL1A1	collagen, type 1, alpha 1	0.008	0.408
513	6595	SMARCA2	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 2	0.037	0.363
514	9334	B4GALT5	UDP-GalibetaGlcNAc beta 1,4- galactosyltransferase, polypeptide 5	<0.001	0.454
515	5743	PTGS2	prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase)	0.005	−0.991
516	3725	JUN	jun proto-oncogene	0.03	0.309
517	9689	BZW1	basic leucine zipper and W2 domains 1	0.003	−0.506
518	8613	PPAP2B	phosphatidic acid phosphatase type 2B	<0.001	0.545
519	54579	UGT1A5	UDP glucuronosyltransferase 1 family, polypeptide 45	0.012	0.39
520	84447	SYVN1	synovial apoptosis inhibitor 1, synoviolin	<0 001	−1.573
521	146225	CMTM2	CKLF-like MARVEL transmembrane domain containing 2	0.032	0.32

TABLE 6

511 genes differentially expressed in MSC non-exposed in comparison with cells exposed to TCM from sample 5 in comparison with non-exposed cells. The magnitude of the expression change is represented as the logarithm of the fold change.

	GeneID	Name	Description	PValue	Log2FC
1	54769	DIRAS2	DIRAS family, GTP-binding RAS-like 2	0.002	0.643
2	9631	NUP155	nucleoporin 155 kDa	0.024	0.337
3	1314	COPA	coatomer protein complex, subunit alpha	0.029	−0.303
4	25912	C1orf43	chromosome 1 open reading frame 43	0.022	−0.333
5	23516	SLC39A14	solute carrier family 39 (zinc vansporter), member 14	0.022	−0.343
6	11137	PWP1	PWP1 homolog (*S. cerevisiae*)	0.02	−0.317
7	54623	PAF1	Paf1, RNA polymerase II associated factor, homolog (*S. cerevisiae*)	0.049	−0.451
8	92609	TIMM50	translocase of inner mitochondrial membrane 50 homolog (*S. cerevisiae*)	0.008	0.481
9	100133941	CD24	CD24 molecule	<0.001	0.574
10	57730	ANKRD36B	ankyrin repeat domain 36B	0.022	0.43
11	1968	EIF2S3	eukaryotic translation initiation factor 2, subunit 3 gamma, 52 kDa	0.025	−0.422
12	85445	CNTNAP4	contactin associated protein-like 4	0.024	0.353
13	6782	FISPA13	heat shock protein 70 kDa family, member 13	<0.001	−1.084
14	81626	SHCBP1L	SHC SH2-domain binding protein 1-like	<0.001	0.898
15	2959	GTF2B	general transcription factor 1B	0.004	0.704
16	51278	IER5	immediate early response 5	0.02	0.437
17	54541	DDIT4	DNA-damage-inducible transcript 4	0.001	−0.443
18	2199	FBLN2	fibulin 2	<0.001	0.632
19	3488	IGFBP5	insulin-like 2rowth factor binding protein 5	<0.001	0.722
20	10659	CELF2	CUGBP, Elan-like family member 2	<0.001	0.793
21	50613	UBQLN3	ublquilin 3	0.013	0.406
22	54629	FAM63B	family with secluence similarity 63, member B	0.04	−0.426
23	6396	SEC13	SEC13 homolog (*S. cerevisiae*)	0.009	−0.439
24	51310	SLC22A17	solute carrier family 22, member 17	0.009	0.322
25	4357	MPST	mercaptopyruvate sulfurtransferase	0.044	−1.112
26	10777	ARPP21	cAMP-regulated phosphoprotein, 21 kDa	0.008	−0.403
27	1465	CSRP1	cysteine and glycine-rich protein 1	0.007	0.322
28	391819	KRT18P42	keratin 18 pseudogene 42	0.024	−0.513
29	3954	LETM1	leucine zipper-EF-hand containing transmembrane protein 1	<0.001	−0.524
30	7278	TUBA3C	tubulin, alpha 3c	0.002	0.381
31	5781	PTPN11	protein tyrosine phosphatase, non-receptor type 11	0.024	−0.693
32	2574	GAGE2C	G antigen 20	0.002	0.518
33	10476	ATPSH	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit d	0.014	−0.403
34	5756	TWF1	twinfilin, actin-binding protein, homolog 1 (*Drosophila*)	0.028	−0.796
35	3590	IL11RA	interleukin 11 receptor, alpha	0.024	−0.371
36	8404	SPARCL1	SPARC-like 1 (hevin)	0.007	0.587
37	55062	WIPI1	WD repeat domain, phosphoinositide interacting 1	0.009	−0.486
38	29116	MYLIP	myosin regulatory light chain interacting protein	0.011	0.44
39	55907	CMAS	cytidine monophosphate N-acetylneuraminic acid synthetase	0.01	0.433
40	84661	DPY30	dpy-30 homolog (*C. elegans*)	0.021	0.444
41	55000	TUG1	taurine upregulated 1 (non-protein coding)	0.02	0.446
42	1672	DEFB1	defensin, beta 1	0.009	0.467
43	10769	PLK2	polo-like kinase 2	0.047	0.32
44	2191	FAP	fibroblast activation protein, alpha	0.002	−0.504
45	1312	COMT	catechol-O-methyltransferase	0.048	0.305
46	972	CD74	CD74 molecule, malor histocompatibility complex, class invariant chain	0.007	0.478
47	85414	SLC45A3	solute carrier family 45, member 3	0.013	0.484
48	5579	PRKCB	protein kinase C, beta	0.022	0.583
49	90507	SCRN2	secernin 2	0.05	0.358
50	386677	KRTAP10-1	keratin associated protein 10-1	0.006	−0.387
51	1912	PHC2	polyhomeotic homolog 2 (*Drosophila*)	0.001	−0.84
52	100271071	RPS17P10	ribosomal protein S17 pseudogene 10	0.014	−0.573
53	10961	ERP29	endoplasmic reticulum protein 29	0.024	0.358
54	80161	ASMTL-AS1	ASMTL antisense RNA 1 (non-protein coding)	0.028	−0.326
55	56970	ATXN7L3	ataxin 7-like 3	0.042	−0.333
56	9789	SPC52	signal peptidase complex subunit 2 homolog (*S. cerevisiae*)	0.007	0.455
57	2969	GTF2I	general transcription factor III	0.028	0.345
58	8894	EIF2S2	eukaryotic translation initiation factor 2, subunit 2 beta, 38 kDa	0.05	−0.5
59	8073	PTP4A2	protein tyrosine phosphatase type IVA, member 2	0.016	0.362
60	10099	TSPAN3	tetraspanin 3	0.013	0.384
61	9013	TAF1C	TATA box binding protein (TBP)-associated factor, RNA polymerase I, C, 110 kDa	0.009	−0.387
62	5138	PDE2A	phosphodiesterase 2A, cGMP-stimulated	0.049	0.514
63	3486	IGFBP3	insulin-like growth factor binding protein 3	0.009	0.394
64	467	ATF3	activating transcription factor 3	<0.001	0.777
65	23264	ZC3H7B	zinc finger CCCH-type containing 7B	0.034	0.352
66	51322	WAC	WW domain containing, adaptor with coiled-coil	0.034	0.37
67	7127	TNFAIP2	tumor necrosis factor, alpha-induced protein 2	0.022	0.496
68	54600	UGT1A9	UDP glucuronosyltransferase 1 family, polypeptide A9	0.002	0.51
69	115416	C7orf30	chromosome 7 open reading frame 30	0.035	−0.667
70	64065	PERP	PERP, TP53 apoptosis effector	0.004	0.5
71	10135	NAMPT	nicotinamide phosphoribosyltransferase	0.003	−0.724
72	51460	SFMBT1	Scm-like with four mbt domains 1	0.014	0.46
73	1345	COX6C	cytochrome c oxidase subunit VIc	0.002	0.381

TABLE 6-continued

511 genes differentially expressed in MSC non-exposed in comparison with cells exposed to TCM from sample 5 in comparison with non-exposed cells. The magnitude of the expression change is represented as the logarithm of the fold change.

	GeneID	Name	Description	PValue	Log2FC
74	8778	SIGLEC5	sialic acid binding Ig-like lectin 5	0.022	−0.399
75	3295	HSD1784	hydroxysteroid (17-beta) dehydrogenase 4	0.013	−0.496
76	112936	VPS26B	vacuolar protein sorting 26 homolog B (*S. pombe*)	0.034	0.469
77	284948	SH2D6	SH2 domain containing 6	0.015	−0.446
78	10808	HSPH1	heat shock 105 kDa/110 kDa protein 1	<0.001	0.619
79	64208	POPDC3	popeye domain containing 3	0.012	−0.53
80	56110	PCDHGA5	protocadherin gamma subfamily A, 5	0.009	−0.379
81	23562	CLDN14	claudin 14	0.028	−0.433
82	2323	FLT3LG	fms-related tyrosine kinase 3 ligand	0.03	−0.354
83	8321	FZD1	frizzled homolog 1 (*Drosophila*)	0.007	0.576
84	5270	SERPINE2	serpin peptidase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1), member 2	0.005	−0.4
85	25907	TMEM158	transmembrane protein 158 (gene/pseudogene)	0.01	−0.587
86	1003	CDH5	cadherin 5, type 2 (vascular endothelium)	0.011	0.629
87	9531	BAG3	BCL2-associated athanogene 3	0.001	0.537
88	2824	GPM68	glycoprotein M68	<0.001	0.616
89	478	ATP1A3	ATPase, Na+/K+ transporting, alpha 3 polypeptide	0.009	0.577
90	338799	LOC338799	hypothetical LOC338799	0.003	−0.484
91	5476	CTSA	cathepsin A	0.016	−0.303
92	79137	FAM134A	family with sequence similarity 134, member A	0.014	−0.382
93	221143	N6AMT2	N-6 adenine-specific DNA methyltransferase 2 (putative)	0.016	−0.304
94	3336	HSPE1	heat shock 10 kDa protein 1 (chaperonin 10)	0.002	0.55
95	80279	CDK5RAP3	CDK5 regulatory subunit associated protein 3	0.001	0.493
96	10987	COPS5	COP9 constitutive photomorphogenic homolog subunit 5 (*Arabidopsis*)	0.039	0.34
97	22978	NT5C2	5'-nucleotidase, cytosolic II	0.037	0.35
98	2353	FOS	FBJ murine osteosarcoma viral oncogene homolog	0.001	0.52
99	55228	PNMAL1	PNMA-like 1	0.009	0.594
100	11215	AKAP11	A kinase (PRKA) anchor protein 11	0.012	0.477
101	51727	CMPK1	cytidine monophosphate (UMP-CMP) kinase 1, cytosolic	0.027	−0.405
102	8566	PDXK	pyridoxal (pyridoxine, vitamin B6) kinase	0.013	0.357
103	4884	NPTX1	neuronal pentraxin I	0.003	0.629
104	7485	WRB	tryptophan rich basic protein	0.032	0.35
105	11179	ZNF277	zinc finger protein 277	0.024	−0.543
106	55811	ADCY10	adenylate cyclase 10 (soluble)	0.012	−0.398
107	23070	FTSJD2	FtsJ methyltransferase domain containing 2	0.045	0.32
108	163033	ZNF579	zinc finger protein 579	0.016	−0.319
109	53826	FXYD6	FXYD domain containing ion transport regulator 6	0.004	0.418
110	11170	FAM107A	family with sequence similarity 107, member A	<0.001	0.402
111	8985	PLOD3	procollagen-lysine, 2-oxoglutarate 5-dioxygenase 3	0.02	−0.463
112	1164	CKS2	CDC28 protein kinase regulatory subunit 2	<0.001	0.694
113	388692	LOC388692	hypothetical LOC388692	0.006	0.319
114	8662	EIF3B	eukaryotic translation initiation factor 3, subunit B	0.028	−0.329
115	4673	NAP1L1	nucleosome assembly protein 1-like 1	0.013	0.326
116	23621	BACE1	beta-site APP-cleaving enzyme 1	0.011	−0.367
117	2983	GUCY153	guanylate cyclase 1, soluble, beta 3	0.017	0.309
118	7546	ZIC2	Zic family member 2 (odd-paired homolog, *Drosophila*)	0.035	0.458
119	51617	HMP19	HMP19 protein	0.01	0.438
120	54657	UGT1A4	UDP glucuronosyltransferase 1 family, polypeptide A4	0.034	0.329
121	23786	BCL2L13	BCL2-like 13 (apoptosis facilitator)	0.019	0.469
122	23209	MLC1	megalencephalic leukoencephalopathy with subcortical cysts 1	0.026	0.44
123	3032	HADHB	hydroxyacyl-CoA dehydrogenase/3-keteacyl-CoA thiolase/enoyl-CoA hydratase (trifunctional protein), beta subunit	0.008	−0.332
124	351020	LOC391020	interferon induced transmembrane protein pseudogene	0.009	−0.318
125	7458	EIF4H	eukaryotic translation mitation factor 4H	0.01	−0.302
126	283971	CLEC18C	C-type lectin domain family 18, member C	0.022	0.327
127	7102	TSPAN7	tetraspanin 7	0.006	0.57
128	4783	NFIL3	nuclear factor, interleukin 3 regulated	0.004	−0.483
129	10859	LILRB1	leukocyte immunoglobulin-like receptor, subfamily B (with TM and ITIM domains), member 1	0.024	−0.483
130	284257	BOD1P	biorientation of chromosomes in cell division 1 pseudogene	0.01	0.51
131	813	CALU	calumenin	0.015	−0.469
132	23352	UBR4	ubiquitin protein ligase E3 component n-recognin 4	0.014	−0.33
133	2697	GJA1	gap junction protein, alpha 1, 43 kDa	0.038	−0.423
134	6119	RPA3	replication protein A3, 14 kDa	0.017	0.379
135	57730	ANKRD36B	ankyrin repeat domain 36B	0.011	0.368
136	112714	TUBA3E	tubulin, alpha 3e	0.011	0.418
137	10439	OLFM1	olfactomedin 1	0.009	0.48
138	51733	UPB1	ureidopropionase, beta	0.045	−0.323
139	7175	TPR	translocated promoter region (to activated MET oncogene)	0.022	0.417
140	25840	METTL7A	methyltransferase like 7A	0.017	0.481
141	26528	DAZAP1	DAZ associated protein 1	0.007	0.491
142	7058	THBS2	thrombospondin 2	0.026	−0.325
143	9452	ITM2A	integral membrane protein 2A	0.002	0.748
144	65055	REEP1	receptor accessory protein 1	0.001	0.516

TABLE 6-continued

511 genes differentially expressed in MSC non-exposed in comparison with cells exposed to TCM from sample 5 in comparison with non-exposed cells. The magnitude of the expression change is represented as the logarithm of the fold change.

	GeneID	Name	Description	PValue	Log2FC
145	10531	PITRM1	pitrilysin metallopeptidase 1	0.006	0.334
146	79791	FBXO31	F-box protein 31	0.023	0.329
147	3936	LCP1	lymphocyte cytosolic protein 1 (L-plastin)	0.01	0.646
148	9536	PTGES	prostaglandin E synthase	0.005	−0.708
149	83657	DYNLRB2	dynein, light chain, roadblock-type 2	0.027	0.337
150	84681	HINT2	histidine triad nucleotide binding protein 2	0.036	0.314
151	51231	VRK3	vaccinia related kinase 3	0.025	−0.686
152	26048	ZNF500	zinc finger protein 500	0.003	−0.332
153	151011	SEPT10	septin 10	0.01	−0.545
154	26749	GAGE2E	G antigen 2E	0.007	0.426
155	7644	ZNF91	zinc finger protein 91	0.04	0.323
156	231	AKR1B1	aido-keto reductase family 1, member B1 (aldose reductase)	<0.001	−0.53
157	501	ALDH7A1	aldehyde dehydrogenase 7 family, member A1	0.002	−0.511
158	4131	MAP1B	microtubule-associated protein 1B	0.024	0.44
159	4358	MPV17	MpV17 mitochondrial inner membrane protein	0.004	−0.43
160	5913	RAPSN	receptor-associated protein of the synapse	0.009	−0.378
161	54881	TEX10	testis expressed 10	0.003	−0.473
162	8460	TPST1	tyrosylprotein sulfotransferase 1	0.005	−0.451
163	60312	AFAP1	actin filament associated protein 1	0.011	−0.436
164	84817	TXNDC17	thioredoxin domain containing 17	0.031	0.331
165	26608	TBL2	transducin (beta)-like 2	<0.001	0.677
166	55753	OGDHL	oxoglutarate dehydrogenase-like	0.003	0.441
167	10472	ZNF238	zinc finger protein 238	0.011	0.477
168	1164	CKS2	CDC28 protein kinase regulatory subunit 2	<0.001	0.513
169	83547	RILP	Rab interacting lysosomal protein	0.042	−0.466
170	274	13161	bridging integrator 1	0.042	−0.401
171	89958	C9orf140	chromosome 9 open reading frame 140	0.034	−0.341
172	653639	LPLA2P1	lysophospholipase II pseudogene 1	0.036	−0.37
173	51616	TAF9B	TAF9B RNA polymerase II, TATA box binding protein (TBP)-associated factor, 31 kDa	0.029	0.366
174	1478	CSTF2	cleavage stimulation factor, 3'pre-RNA, subunit 2, 64 kDa	0.048	−0.549
175	22913	RALY	RNA binding protein, autoantigenic (hnRNP-associated with lethal yellow homolog (mouse))	0.012	−0.585
176	10808	HSPH1	heat shock 105 kDa/110 kDa protein 1	0.037	−0.313
177	196	AHR	aryl hydrocarbon receptor	<0.001	−0.753
178	1429	CRYZ	crystallin, zeta (quinone reductase)	0.017	0.385
179	65009	NDRG4	NDRG family member 4	0.001	0.472
180	126823	KLHDC9	kelch domain containing 9	0.039	0.402
181	2938	GSTA1	glutathione S-transferase alpha 1	0.018	0.392
182	3048	HBG2	hemoglobin, gamma G	0.009	0.375
183	2171	FABP5	fatty acid binding protein 5 (psoriasis-associated)	0.013	0.328
184	5110	PCMT1	protein-L-isoaspartate (D-aspartate) O-methyltransferase	0.005	−0.614
185	3308	HSPA4	heat shock 70 kDa protein 4	0.047	−0.439
186	4054	LTBP3	latent transforming growth factor beta binding protein 3	0.031	−0.768
187	51693	TRAPPC2L	trafficking protein particle complex 2-like	0.028	−0.372
188	7980	TFPI2	tissue factor pathway inhibitor 2	<0.001	−1.085
189	146330	FBXL16	F-box and leucine-rich repeat protein 16	0.047	0.524
190	7494	XBP1	X-box binding protein 1	0.008	−0.306
191	51655	RASD1	RAS, dexamethasone-induced 1	<0.001	0.762
192	9766	KIAA0247	KIAA0247	0.007	−0.483
193	27288	RBMXL2	RNA binding motif protein, X-linked-like 2	0.037	0.405
194	56731	SLC2A4RG	SLC2A4 regulator	0.015	−1.281
195	10971	YWHAQ	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, theta polypeptide	0.003	0.305
196	9689	BZW1	basic leucine zipper and W2 domains 1	0.004	−0.35
197	9240	PNMA1	paraneoplastic antigen MA1	0.024	0.37
198	23270	TSPYL4	TSPY-like 4	0.037	0.305
199	900	CCNG1	cyclin G1	0.01	−0.378
200	10542	HBXIP	hepatitis B virus x interacting protein	0.005	0.354
201	10147	SUGP2	SURP and G patch domain containing 2	0.035	0.309
202	128218	TMEM125	transmembrane protein 125	0.002	0.645
203	7873	MANF	mesencephalic astrocyte-derived neurotrophic factor	<0.001	−0.526
204	286204	CRB2	crumbs homolog 2 (*Drosophila*)	0.035	−0.305
205	7179	TPTE	transmembrane phosphatase with tensin homology	0.04	0.418
206	10523	CHERP	calcium homeostasis endoplasmic reticulum protein	0.017	−0.341
207	64750	SMURF2	SMAD specific E3 ubiquitin protein ligase 2	<0.001	−0.42
208	5791	PTPRE	protein tyrosine phosphatase, receptor type E	0.012	−0.333
209	51533	PHF7	PHD finger protein 7	0.004	0.444
210	23476	BRD4	bromodomain containing 4	0.043	−0.319
211	9690	UBE3C	ubiquitin protein ligase E3C	0.031	−0.375
212	51141	INSIG2	insulin induced gene	0.004	−0.417
213	84935	C13orf33	chromosome 13 open reading frame 33	<0.001	−0.71
214	9554	SEC22B	SEC22 vesicle trafficking protein homolog B (*S. cerevisiae*) (gene/pseudogene)	0.034	−0.347

TABLE 6-continued

511 genes differentially expressed in MSC non-exposed in comparison with cells exposed to TCM from sample 5 in comparison with non-exposed cells. The magnitude of the expression change is represented as the logarithm of the fold change.

	GeneID	Name	Description	PValue	Log2FC
215	114907	FBXO32	F-box protein 32	0.034	−0.333
216	84532	ACSS1	acyl-CoA synthetase short-chain family member 1	0.03	0.356
217	4162	MCAM	melanoma cell adhesion molecule	0.017	−0.436
218	5726	PGD	phosphogluconate dehydrogenase	0.019	−0.378
219	7307	U2AF1	U2 small nuclear RNA auxiliary factor 1	0.027	0.312
220	3312	HSPA8	heat shock 70 kDa protein 8	0.004	0.343
221	8209	C21orf33	chromosome 21 open reading frame 33	0.035	−0.36
222	127933	UHMK1	U2AF homology motif (UHM) kinase 1	<0.001	−0.579
223	55588	MED29	mediator complex subunit 29	0.023	−0.375
224	84525	HOPX	HOP homeobox	0.024	0.464
225	4598	MVK	mevalonate kinase	0.038	−0.316
226	8459	TPST2	tyrosylprotein sulfotransferase 2	0.003	−0.362
227	10079	ATP9A	ATPase ciass II, type 9A	0.015	−0.337
228	8742	TNFSF12	tumor necrosis factor (ligand) superfamily, member 12	0.046	−0.405
229	5045	FURIN	furin (paired basic amino acid cleaving enzyme)	0.028	−0.367
230	267	AMFR	autocrine motility factor receptor	0.005	−0.418
231	6281	3100910	S100 calcium bnding proten A10	0.002	0.425
232	358	AQP1	aquaporin 1 (Colton blood group)	0.007	0.342
233	9070	ASH2L	ash2 (absent, small, or homeotic)-like (*Drosophila*)	0.024	−0.507
234	2939	GSTA2	glutathione S-transferase alpha 2	0.003	0.544
235	29968	PSAT1	phosphoserine aminotransferase 1	0.003	0.524
236	151579	BZW1P2	basic leucine zipper and W2 domains 1 pseudogene 2	0.001	−0.406
237	284942	RPL23AP82	ribosomal protein L23a pseudogene 82	0.017	−0.444
238	11079	RER1	RER1 retention in endoplasmic reticulum 1 homolog (*S. cerevisiae*)	0.004	−0.376
239	9920	KBTBD11	kelch repeat and BTB (POZ) domain containing 11	0.049	0.327
240	2628	GATM	glycine amidinotransferase (L-arginine glycine amidinotransferase)	0.017	0.464
241	115207	KCTD12	potassium channel tetramerisation domain containing 12	0.001	−0.575
242	56113	PCDHGA2	protocadherin gamma subfamily A, 2	0.026	−0.347
243	84922	FIZ1	FLT3-interacting zinc finger 1	0.006	−0.369
244	4833	NME4	non-metastatic cells 4, protein expressed in	0.049	−0.337
245	140459	ASB6	ankyrin repeat and SOCS box containing 6	0.002	−0.528
246	6427	SRSF2	serine/arginine-rich splicing factor 2	0.031	0.312
247	4553	TRNA	tRNA	<0.001	0.801
248	55002	TMCO3	transmembrane and coiled-coil domains 3	0.002	−0.387
249	4853	NOTCH2	notch 2	0.008	−0.38
250	29015	SLC43A3	solute carrier family 43, member 3	0.003	−0.625
251	58986	TMEM8A	transmembrane protein 89	0.045	−0.393
252	51719	CAB39	calcium binding protein 39	0.021	−0.318
253	10730	YME1L1	YME1-like 1(*S. cerevisiae*)	0.033	−0.36
254	100506243	KRBOX1	KRAB box domain containing 1	0.008	0.415
255	51533	PHF7	PHD finger protein 7	0.008	0.322
256	27044	SND1	staphylococcal nuclease and tudor domain containing 1	0.008	−0.487
257	9547	CXCL14	chemokine (C-X-C motif) ligand 14	0.014	0.437
258	83548	COG3	component of oligomeric golgi complex 3	0.032	−0.362
259	5164	PDK2	pyruvate dehydrogenase kinase isozyme 2	0.024	−0.357
260	79140	CCDC28B	coiled-coil domain containing 28B	0.031	−0.309
261	5539	PPY	pancreatic polypeptide	0.024	0.869
262	5934	RBL2	retinoblastoma-like 2 (p130)	0.044	−0.327
263	440533	PSG8	pregnancy specific beta-1-glycoprotein 8	0.011	−0.376
264	283768	GOLGA8G	golgin A8 family, member G	0.002	0.419
265	7196	TRNAG2	transfer RNA glycine 2 (anticodon GCC)	<0.001	−1.44
266	51339	DACT1	dapper, antagonist of beta-catenin, homolog 1 (*Xenopus laevis*)	0.009	−0.415
267	2581	GALC	galactosylceramidase	0.015	−0.621
268	4311	MME	membrane metallio-endopeptidase	0.008	−0.343
269	857	CAV1	caveolin 1, caveolae protein, 22 kDa	<0.001	0.511
270	84961	FBXL20	F-box and leucine-rich repeat protein 20	0.049	−0.351
271	1902	LPAR1	lysophosphatidic acid receptor 1	0.024	−0.643
272	9215	LARGE	like-glycosyltransferase	0.015	−0.317
273	84270	C9orf89	chromosome 9 open reading frame 89	0.002	−0.378
274	341032	C11orf53	chromosome 11 open reading frame 53	0.007	−0.584
275	6494	SIPA1	signal-induced proliferation-associated 1	0.032	−0.301
276	51453	RHCG	Rh family, C glycoprotein	0.033	0.301
277	441198	LOC441198	similar to Heat shock cognate 71 kDa protein	0.023	0.302
278	349114	NCRNA00265	non-protein coding RNA 265	0.045	0.303
279	3304	HSPA18	heat shock 70 kDa protein 18	0.001	0.519
280	84791	C1orf97	chromosome 1 open reading frame 97	0.007	0.384
281	84617	TUBB6	tubulin, beta 6	0.006	0.313
282	91012	LASS5	LAG1 homolog, ceramide synthase 5	0.002	−0.517
283	8766	RAB11A	RAB11A, member RAS oncogene family	0.007	−0.352
284	4070	TACSTD2	tumor-associated calcium signal transducer 2	0.009	0.428
285	58515	SELK	selenoprotein K	<0.001	−0.517
286	54815	GATAD2A	GATA zinc finger domain containing 2A	0.014	−0.341
287	4920	ROR2	receptor tyrosine kinase-like orphan receptor 2	0.027	−0.312
288	51009	DERL2	Der1-like domain family member 2	0.004	−0.326

TABLE 6-continued

511 genes differentially expressed in MSC non-exposed in comparison with cells exposed to TCM from sample 5 in comparison with non-exposed cells. The magnitude of the expression change is represented as the logarithm of the fold change.

	GeneID	Name	Description	PValue	Log2FC
289	335	APOA1	apolipoprotein A-1	0.043	−0.304
290	340198	IFITM4P	interferon induced transmembrane protein 4 pseudogene	0.016	0.431
291	57214	KIAA1199	KIAA1199	0.041	−0.602
292	51232	CRIM1	cysteine rich transmembrane BMP regulator 1 (chordin-like)	0.046	0.549
293	124773	C17orf64	chromosome 17 open reading frame 64	0.007	0.398
294	56114	PCDHGA1	protocadherin gamma subfamily A, 1	0.012	−0.424
295	112483	SAT2	spermidine/spermine N1-acetyltransferase family member 2	0.001	−0.441
296	2000	ELF4	E74-like factor 4 (ets domain transcription factor)	0.014	−0.362
297	1645	AKR1C1	aldo-keto reductase family 1, member C1 (dihydrodiol dehydrogenase 1; 20-alpha (3-alpha)-hydroxysteroid dehydrogenase)	0.003	−0.633
298	10383	TUBB2C	tubulin, beta 2C	0.002	0.343
299	6888	TALDO1	transaidolase 1	0.035	−0.33
300	5902	RANBP1	RAN binding protein 1	0.005	−0.474
301	51030	FAM18B1	family with sequence similarity 18, member B1	0.016	−0.307
302	7259	TSPYL1	TSPY-like 1	0.014	0.365
303	134147	CMBL	carboxymethylenebutenolidase homolog (*Pseudomonas*)	0.024	0.302
304	6303	SAT1	spermidine/spermine N1-acetyltransferase 1	0.011	−0.318
305	83871	RAB34	RAB34, member RAS oncogene family	0.003	−0.338
306	6542	SLC7A2	solute carrier family 7 (cationic amino acid transporter, y+ system), member 2	0.005	−0.304
307	22936	ELL2	elongation factor, RNA polymerase II, 2	<0.001	−0.709
308	58508	MLL3	myeloid/lymphoid or mixed-lineage leukemia 3	0.017	−0.466
309	5111	PCNA	proliferating cell nuclear antigen	0.037	0.404
310	1827	RCAN1	regulator of calcineurin 1	<0.001	−0.676
311	8720	MBTPS1	membrane-bound transcription factor peptidase, site 1	0.045	−0.329
312	8490	RGS5	regulator of G-protein signaling 5	0.02	0.465
313	56674	TM EM98	TMEM9 domain family, member 8	0.011	0.4
314	6713	SQLE	squalene epoxidase	0.009	−0.393
315	3434	IFIT1	interferon-induced protein with tetratricopeptide repeats 1	<0.001	0.422
316	3192	HNRNPU	heterogeneous nuclear ribonucleoprotein U (scaffold attachment factor A)	0.009	0.324
317	5916	RARG	retinoic acid receptor, gamma	0.004	−0.65
318	84232	MAF1	MAF1 homolog (*S. cerevisiae*)	0.022	0.325
319	729148	NUS1P1	nuclear undecaprenyl pyrophosphate synthase 1 homolog (*S. cerevisiae*) pseudogene 1	0.016	−0.422
320	5611	DNAIC3	DnaI (Hsp40) homolog, subfamily C, member 3	<0.001	−0.92
321	151636	DTX3L	deltex 3-like (*Drosophila*)	0.042	0.664
322	83447	SLC25A31	solute carrier family 25 (mitochondrial carrier adenine nucleotide translocator), member 31	0.044	0.42
323	171169	SPACA4	sperm acrosome associated 4	0.038	−0.452
324	51652	VPS24	vacuolar protein sorting 24 homolog (*S. cerevisiae*)	0.002	0.419
325	64215	DNAJC1	DnaJ (Hsp40) homolog, subfamily C, member 1	0.004	−0.489
326	63916	ELMO2	engulfment and cell motility 2	0.03	−0.415
327	4170	MCL1	myeloid cell leukemia sequence 1 (BCL2-related)	<0.001	0.554
328	10123	ARL4C	ADP-ribosylation factor-like 4C	0.007	0.383
329	3324	HSP90AA2	heat shock protein 90 kDa alpha (cytosolic), class A member 2	0.002	0.398
330	10285	SMNDC1	survival motor neuron domain containing 1	0.036	−0.761
331	54538	ROBO4	roundabout homolog 4, magic roundabout (*Drosophila*)	0.033	0.375
332	133957	CCDC127	coiled-coil domain containing 127	0.037	0.327
333	7280	TUBB2A	tubulin, beta 2A	<0.001	0.62
334	1116	CHI3L1	chitinase 3-like 1 (cartilage glycoprotein-39)	0.008	−0.348
335	4256	MGP	matrix Gla protein	0.003	0.448
336	4926	NUMA1	nuclear mitotic apparatus protein 1	0.038	−0.306
337	3748	KCNC3	potassium voltage-gated channel, Shaw-related subfamily member 3	0.008	−0.378
338	90737	PAGE5	P antigen family, member 5 (prostate associated)	0.025	0.315
339	84707	BEX2	brain expressed X-linked 2	0.034	0.326
340	5901	RAN	RAN, member RAS oncogene family	0.001	0.324
341	56927	GPR108	G protein-coupled receptor 108	0.043	−0.471
342	7832	BTG2	BTG family, member 2	0.046	0.316
343	23174	ZCCHC14	zinc finger, CCHC domain containing 14	0.017	0.336
344	60592	SCOC	short coiled-coil protein	0.005	0.413
345	115992	RNF166	ring finger protein 166	0.005	−0.692
346	604	BCL6	B-cell CLL/lymphoma 6	0.012	−0.512
347	8537	BCA51	breast carcinoma amplified sequence 1	0.016	0.331
348	432	ASGR1	asialoglycoprotein receptor	0.045	0.386
349	7542	ZFPL1	zinc finger protein-like 1	0.017	−0.514
350	57570	TRMT5	TRM5 tRNA methyltransferase 5 homolog (*S. cerevisiae*)	0.006	0.324
351	4567	TRNL1	tRNA	0.033	0.316
352	83880	EIF3FP2	eukaryotic translation initiation factor 3, subunit F pseudogene 2	0.012	−0.44
353	3303	HSPA1A	heat shock 70 kDa protein 1A	0.002	0.633
354	63933	CCDC90A	coiled-coil domain containing 90A	0.035	−0.777
355	81839	VANGL1	vang-like 1 (van gogh, *Drosophila*)	0.045	−0.378
356	220988	HNRNPA3	heterogeneous nuclear ribonucleoprotein A3	<0.001	0.477
357	51454	GULP1	GULP engulfment adaptor PTB domain containing 1	0.007	−0.535
358	949	SCARB1	scavenger receptor class B, member 1	<0.001	−0.582

TABLE 6-continued

511 genes differentially expressed in MSC non-exposed in comparison with cells exposed to TCM from sample 5 in comparison with non-exposed cells. The magnitude of the expression change is represented as the logarithm of the fold change.

	GeneID	Name	Description	PValue	Log2FC
359	9709	HERPUD1	homocysteine-inducible endoplasmic reticulum stress-inducible, ubiquitin-like domain member 1	0.011	−0.325
360	85021	REPS1	RALBP1 associated Eps domain containing 1	0.022	−0.627
361	26273	FBXO3	F-box protein 3	0.002	0.34
362	5481	PPID	peptidylprolyl isomerase D	0.011	0.326
363	359948	IRF2BP2	interferon regulatory factor binding protein 2	0.014	−0.327
364	1728	NQO1	NAD(P)H dehydrogenase, quinone 1	0.048	−0.453
365	3119	HLA-DQB1	major histocornpatibility complex, class II, DQ beta	0.003	0.393
366	2166	FAAH	fatty acid amide hydrolase	0.026	0.381
367	6652	SORD	sorbitol dehydrogenase	0.03	0.353
368	55251	PCMTD2	protein-L-isoaspartate (D-aspartate) O-methyltransferase domain containing 2	0.04	−0.376
369	402562	HNRNPA1P8	heterogeneous nuclear ribonucleoprotein A1 pseudogene 8	0.013	−0.341
370	6428	SRSF3	serine/arginine-rich splicing factor 3	<0.001	0.516
371	55920	RCC2	regulator of chromosome condensation 2	<0.001	0.457
372	10922	FASTK	Fas-activated serine/threonine kinase	0.008	−0.485
373	3295	HSD1784	hydroxysteroid (17-beta) dehydrogenase 4	0.007	−0.593
374	7453	WARS	tryptophanyl-tRNA synthetase	0.045	0.344
375	9823	ARMCX2	armadillo repeat containing, X-linked 2	0.012	−0.476
376	51706	CYB5R1	cytochrome b5 reductase 1	0.041	−0.46
377	51660	BRP44L	brain protein 44-like	0.049	0.302
378	51043	ZBTB7B	zinc finger and BTB domain containing 7B	<0.001	−0.489
379	6892	TAPBP	TAP binding protein (tapasin)	<0.001	−0.727
380	51075	TMX2	thioredoxin-related transmembrane protein 2	0.032	−0.35
381	54617	INO80	INO80 homolog (*S. cerevisiae*)	0.03	−0.434
382	1523	CUX1	cut-like homeobox 1	0.021	−0.413
383	1503	CTPS	CTP synthase	0.02	−0.505
384	7273	TTN	titin	0.002	−0.327
385	2036	EPB41L1	erythrocyte membrane protein band 4.1-like 1	0.043	−0.415
386	8451	CUL4A	cuilin 4A	0.035	−0.331
387	55342	STRBP	spermatid perinuclear RNA binding protein	0.018	−0.427
388	7180	CRISP2	cysteine-rich secretory protein 2	0.005	0.485
389	283902	HTA	hypothetical LOC283902	0.03	−0.347
390	9246	UBE2L6	ubiquitin-conjugating enzyme E2L 6	0.003	0.434
391	6236	RRAD	Ras-related associated with diabetes	<0.001	0.612
392	5209	PFKF83	6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3	0.006	0.361
393	91695	RRP78	ribosomal RNA processing 7 homolog B (*S. cerevisiae*)	0.008	−0.333
394	2938	GSTA1	glutathione S-transferase alpha 1	0.006	0.334
395	3550	IK	IK cytokine, down-regulator of HLA II	0.012	−0.366
396	3190	HNRNPK	heterogeneous nuclear ribonucleoprotein K	0.005	−0.337
397	8277	TKTL1	transketolase-like 1	0.006	0.332
398	1982	EIF4G2	eukaryotic translation initiation factor 4 gamma, 2	<0.001	0.436
399	6711	SPTBN1	spectrin, beta, non-erythrocytic 1	0.009	0.506
400	116254	C6orf72	chromosome 6 open reading frame 72	<0.001	−0.42
401	51187	RSL24D1	ribosomal L24 domain containing 1	0.003	−0.406
402	7170	TPM3	tropomyosin 3	0.028	−0.387
403	3459	IFNGR1	interferon gamma receptor 1	0.002	−0.481
404	246243	RNASEH1	ribonuclease H1	0.01	−0.302
405	29880	ALG5	asparagine-linked glycosylation 5, dolichyl-phosphate beta-glucosyltransferase homolog (*S. cerevisiae*)	0.008	−0.308
406	55197	RPRD1A	regulation of nuclear pre-mRNA domain containing 1A	0.017	−0.405
407	81926	FAM108A1	family with sequence similarity 108, member A1	0.037	0.35
408	9670	IPO13	importin 13	0.033	−0.408
409	92558	CCDC64	coiled-coil domain containing 64	0.019	−0.447
410	5698	1551139	proteasome (prosome, macropain) subunit, beta type, 9 (large multifunctional peptidase 2)	0.003	0.409
411	283131	NEAT1	nuclear paraspeckle assembly transcript 1 (non-protein coding)	0.009	−0.309
412	5202	PFDN2	prefoldin subunit 2	0.004	−0.433
413	43	ACHE	acetylcholinesterase	0.022	−0.423
414	79940	C6orf155	chromosome 6 open reading frame 155	0.046	−0.356
415	10330	CNPY2	canopy 2 homolog (zebrafish)	0.023	−0.348
416	3500	IGHG1	immunoglobulin heavy constant gamma 1 (G1m marker)	0.021	0.53
417	123	PLIN2	perilipin 2	0.045	−0.347
418	3184	HNRNPD	heterogeneous nuclear ribonucleoprotein D (AU-rich element RNA binding protein 1, 37 kDa)	0.046	0.383
419	2919	CXCL1	chemokine (C-X-C motif) ligand 1 (melanoma growth stimulating activity, alpha)	0.012	−0.886
420	51763	INPPSK	inositol polyphosphate-5-phosphatase K	0.006	−0.313
421	27020	NPTN	neuroplastin	0.015	0.334
422	7052	TGM2	transglutaminase 2 (C polypeptide, protein-glutamine-gamma-glutamyltransferase)	<0.001	−0.594
423	2332	FMR1	fraglie X mental retardation 1	0.041	0.306
424	9792	SERTAD2	SERTA domain containing 2	0.045	−0.363

TABLE 6-continued

511 genes differentially expressed in MSC non-exposed in comparison with cells exposed to TCM from sample 5 in comparison with non-exposed cells. The magnitude of the expression change is represented as the logarithm of the fold change.

	GeneID	Name	Description	PValue	Log2FC
425	10507	SEMA4D	sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4D	0.034	−0.814
426	3976	LIF	leukemia inhibitory factor (cholinergic differentiation factor)	0.001	−0.622
427	4085	MAD2L1	MAD2 mitotic arrest deficient-like 1 (yeast)	0.002	−0.433
428	84879	MFSD2A	major facilitator superfamily domain containing 2A	0.029	−0.32
429	203068	TUBB	tubulin, beta	0.006	−0.386
430	5721	PSME2	proteasome (prosome, macropain) activator subunit 2 (PA28 beta)	0.002	0.874
431	55140	ELP3	elongation protein 3 homolog (*S. cerevisiae*)	0.023	0.406
432	9043	SPAG9	sperm associated antigen 9	0.015	−0.44
433	57216	VANGL2	vang-like 2 (van gogh, *Drosophila*)	0.023	−0.459
434	54963	UCKL1	uridine-cytidine kinase 1-1ike 1	0.023	−0.39
435	51495	PTPLAD1	protein tyrosine phosphatase-like A domain containing 1	0.022	−0.316
436	199746	U2AF1L4	U2 small nuclear RNA auxiliary factor 1-like 4	0.021	0.379
437	10555	AGPAT2	1-acylglycerol-3-phosphate O-acyltransferase 2 (lysophosphatidic acid acyltransferase, beta)	0.015	0.333
438	8650	NUMB	numb homolog (*Drosophila*)	0.013	−0.374
439	6432	SRSF7	serine/arginine-rich splicing factor 7	0.015	0.388
440	5128	CDK17	cyclin-dependent kinase 17	0.007	0.514
441	5507	PPP1R3C	protein phosphatase 1, regulatory (inhibitor) subunit 3C	0.009	0.518
442	56937	PMEPA1	prostate transmembrane protein, androgen induced 1	0.017	−0.381
443	11189	CELF3	CUGBP, Elav-like family member 3	0.031	0.324
444	51635	DHRS7	dehydrogenase/reductase (SDR family) member 7	0.008	−0.352
445	29085	PHPT1	phosphohistidine phosphatase 1	0.031	0.31
446	64777	RMND5B	required for meiotic nuclear division 5 homolog B (*S. cerevisiae*)	0.039	−0.302
447	284613	CYB561D1	cytochrome b-561 domain containing 1	0.024	−0.464
448	665	BNIP3L	BCL2/adenovirus E1B 19 kDa interacting protein 3-like	0.027	−0.309
449	391570	LOC391670	heterogeneous nuclear ribonucleoprotein A1 pseudogene	0.042	0.343
450	51022	GLRX2	glutaredoxin 2	0.016	−0.37
451	3320	HSP90AA1	heat shock protein 90 kDa alpha (cytosolic), class A member 1	0.038	0.363
452	56106	PCDHGA10	protocadherin gamma subfamily A, 10	0.019	−0.337
453	56160	NDNL2	needin-like 2	0.019	−0.327
454	2791	GNG11	guanine nucleotide binding protein (G protein), gamma 11	0.023	−0.391
455	64834	ELOVL1	elongation of very long chain fatty acids (FEN1/Elo2, SUR4/Elo3, yeast)-like 1	0.007	−0.55
456	10749	KIF1C	kinesin family member 1C	0.003	0.526
457	3336	HSPE1	heat shock 10 kDa protein 1 (chaperonin 10)	0.003	0.417
458	84818	IL17RC	interleukin 17 receptor C	0.009	−0.306
459	5511	PPP1R8	protein phosphatase 1, regulatory (inhibitor) subunit 8	0.032	−0.318
460	134492	NUDCD2	NudC domain containing 2	0.006	−0.557
461	23576	DDAH1	dimethylarginine dimethylaminohydrolase 1	0.008	0.359
462	5156	PDGF8A	platelet-derived growth factor receptor, alpha polypeptide	0.032	−0.457
463	8831	SYNGAP1	synaptic Ras GTPase activating protein 1	0.031	−0.324
464	9600	PITPNM1	phosphatidylinositol transfer protein membrane associated 1	0.007	−0.354
465	1800	DPEP1	dipeptidase 1 (renal)	0.002	−0.403
466	79924	ADM2	adrenomedullin 2	0.031	−0.316
467	2346	FOLH1	folate hydrolase (prostate-specific membrane antigen) 1	0.007	−0.376
468	2787	GNGS	guanine nucleotide binding protein (G protein), gamma 5	0.025	0.361
469	23067	SETD1B	SET domain containing 1B	<0.001	−0.351
470	23042	PDXDC1	pyridoxal-dependent decarboxylase domain containing 1	0.022	−0.302
471	84961	FBXL20	F-box and leucine-rich repeat protein 20	0.026	0.302
472	2992	GYG1	glycogenin 1	0.008	0.468
473	3987	LIMS1	LIM and senescent cell antigen-like domains 1	0.044	−0.357
474	6426	SRSF1	serine/arginine-rich splicing factor 1	0.04	0.7
475	4616	GADD45B	growth arrest and DNA-damage-inducible, beta	0.005	0.438
476	27175	TUBG2	tubulin, gamma 2	0.046	−0.377
477	51187	RSL24D1	ribosomal L24 domain containing 1	0.004	−0.607
478	29081	METTL5	methyltransferase like 5	0.031	−0.414
479	23167	EFR3A	EFR3 homolog A (*S. cerevisiae*)	0.045	−0.371
480	4071	TM4SF1	transmembrane 4 L six family member 1	0.002	−0.416
481	1316	KLF6	Kruppel-like factor 6	0.003	0.418
482	84951	TNS4	tensin 4	0.046	−0.403
483	8668	EIF3I	eukaryotic translation initiation factor 3, subunit I	0.039	−0.381
484	223082	ZNRF2	zinc and ring finger 2	0.036	0.336
485	64778	FNDC3B	fibronectin type III domain containing 3B	0.002	−0.529
486	219654	ZCCHC24	zinc finger, CCHC domain containing 24	0.002	−0.416
487	11098	PRSS23	protease, serine, 23	<0.001	0.677
488	27106	ARRDC2	arrestin domain contaning 2	0.009	−0.412
489	8547	FCN3	ficolin (collagen/fibrinogen domain containing) 3 (Hakata antigen)	0.028	0.365
490	11067	C10orf10	chromosome 10 open reading frame 10	0.042	−0.318
491	7112	TMPO	Thymopoietin	0.048	−0.391
492	84231	TRAF7	TNF receptor-associated factor 7	0.029	−0.458
493	378	ARF4	ADP-ribosylation factor 4	0.015	0.34
494	3337	DNAJB1	DnaJ (Hsp40) homolog, subfamily B, member 1	0.008	0.449
495	10409	BASP1	brain abundant, membrane attached signal protein 1	0.027	−0.314

TABLE 6-continued

511 genes differentially expressed in MSC non-exposed in comparison with cells exposed to TCM from sample 5 in comparison with non-exposed cells. The magnitude of the expression change is represented as the logarithm of the fold change.

	GeneID	Name	Description	PValue	Log2FC
496	8543	LMO4	LIM domain only 4	0.015	−0.314
497	55352	C17orf79	chromosome 17 open reading frame 79	0.037	0.398
498	148229	ATP883	ATPase, aminophospholipid transporter, class I, type 8B, member 3	0.043	−0.312
499	10135	NAMPT	nicotinamide phosphoribosyltransferase	0.017	−0.536
500	10734	STAG3	stromal antigen 3	0.029	0.336
501	3312	HSPA8	heat shock 70 kDa protein 8	<0.001	−0.455
502	5743	PTGS2	prostaglandin-endoperoxide synthase 2 (prostaglandinG/H synthase and cyclooxygenase)	0.026	−0.739
503	3476	IGBP1	immunoglobulin (CD79A) binding protein 1	0.027	−0.351
504	9689	BZW1	basic leucine zipper and W2 domains 1	0.045	−0.315
505	3638	INSIG1	insulin induced gene 1	<0.001	−0.628
506	3340	NDST1	N-deacetylase/N-sulfotransferase (heparan glucosaminyl) 1	0.028	0.437
507	84447	SYVN1	synovial apoptosis inhibitor 1, synoviolin	<0.001	−1.048
508	114971	PTPMT1	protein tyrosine phosphatase, mitochondrial 1	0.021	−0.394
509	9415	FADS2	fatty acid desaturase 2	0.003	−0.548
510	26227	PHGDH	phosphoglycerate dehydrogenase	0.01	−0.367
511	10360	NPM3	nucleophosmin/nucleoplasmin 3	0.048	−0.408

TABLE 7

Receptors expressed in control group (MSC non-exposed) and that recognize soluble factors identified in HCC samples.

EntrezID	Name	Description
1234	CCR5	*Homo sapiens* chemokine (C-C motif) receptor 5 (CCR5), mRNA.
1236	CCR7	*Homo sapiens* chemokine (C-C motif) receptor 7 (CCR5), mRNA.
10803	CCR9	*Homo sapiens* chemokine (C-C motif) receptor 9 (CCR9), transcript variant A, mRNA.
960	CD44	*Homo sapiens* CD44 antigen (homing function and Indian blood group system) (CD44), transcript variant 1, mRNA.
967	CD63	*Homo sapiens* CD63 antigen (melanoma 1 antigen) (CD63), mRNA.
972	CD74	*Homo sapiens* CD74 antigen (invariant polypeptide of major histocompatibility complex, class II antigen-associated) (CD74) mRNA
1524	CX3CR1	*Homo sapiens* chemokine (C-X3-C motif) receptor 1 (CX3CR1), mRNA.
3579	CXCR2	*Homo sapiens* interleukin 8 receptor, beta (IL8RB), mRNA.
7852	CXCR4	*Homo sapiens* chemokine (C-X-C motif) receptor 4 (CXCR4), transcript variant 1, mRNA.
57007	CXCR7	*Homo sapiens* chemokine orphan receptor 1 (CMKOR1), mRNA.
1956	EGFR	*Homo sapiens* epidermal growth factor receptor (erythroblastic leukemia viral (v-erb-b) oncogene homolog, avian) (EGFR), transcript variant 1, mRNA.
2022	ENG	*Homo sapiens* endoglin (Osler-Rendu-Weber syndrome 1) (ENG), mRNA.
2260	FGFR1	*Homo sapiens* fibroblast growth factor receptor 1 (fms-related tyrosine kinase 2, Pfeiffer syndrome) (FGFR1), transcript variant 1, mRNA.
2263	FGFR2	*Homo sapiens* fibroblast growth factor receptor 2 (FGFR2). transcript variant 10, mRNA.
2263	FGFR2	*Homo sapiens* fibroblast growth factor receptor 2 (FGFR2), transcript variant 2, mRNA.
2261	FGFR3	*Homo sapiens* fibroblast growth factor receptor 3 (achondroplasia, thanatophoric dwarfism) (FGFR3), transcript variant 2, mRNA.
2261	FGFR3	*Homo sapiens* fibroblast growth factor receptor 3 (achondroplasia, thanatophoric dwarfism) (FGFR3), transcript variant 1, mRNA.
2264	FGFR4	*Homo sapiens* fibroblast growth factor receptor 4 (FGFR4), transcript variant 1, mRNA.
2264	FGFR4	*Homo sapiens* fibroblast growth factor receptor 4 (FGFR4), transcript variant 2, mRNA.
2321	FLT1	*Homo sapiens* fms-related tyrosine kinase 1 (vascular endothelial growth factor/vascular permeability factor receptor) (FLT1), mRNA.
3459	IFNGR1	*Homo sapiens* interferon gamma receptor 1 (IFNGR1), mRNA.
3480	IGF1R	*Homo sapiens* insulin-like growth factor 1 receptor (IGF1R), mRNA.
3594	IL12RB1	*Homo sapiens* interleukin 12 receptor, beta 1 (IL12RB1), transcript variant 1, mRNA.
3601	IL15RA	*Homo sapiens* interleukin 15 receptor, alpha (IL15RA), transcript variant 2, mRNA.
3601	IL15RA	*Homo sapiens* interleukin 15 receptor, alpha (IL15RA), transcript variant 1, mRNA.
3554	IL1R1	*Homo sapiens* interleukin 1 receptor, type I (IL1R1), mRNA.
3556	IL1RAP	*Homo sapiens* interleukin 1 receptor accessory protein (IL1RAP), transcript variant 1, mRNA.
3563	IL3RA	*Homo sapiens* interleukin 3 receptor, alpha (low affinity) (IL3RA), mRNA.
3566	IL4R	*Homo sapiens* interleukin 4 receptor (IL4R), transcript variant. 1, mRNA.

TABLE 7-continued

Receptors expressed in control group (MSC non-exposed) and that recognize soluble factors identified in HCC samples.

EntrezID	Name	Description
3570	IL6R	*Homo sapiens* interleukin 6 receptor (IL6R), transcript variant 1, mRNA.
3688	ITGB1	*Homo sapiens* integrin, beta 1 (fibronectin receptor, beta polypeptide, antigen CD29 includes MDF2, MSK32) (ITG81), transcript variant 1D, mRNA.
3688	ITGB1	*Homo sapiens* integrin, beta 1 (fibronectin receptor, beta polypeptide, antigen CD29 includes MDF2, MSK12) (ITGB1), transcript variant 1A, mRNA.
5156	PDGFRA	*Homo sapiens* platelet-derived growth factor receptor, alpha polypeptide (PDGFRA), mRNA.
5159	PDGFRB	*Homo sapiens* platelet-derived growth factor receptor, beta polypeptide (PDGFRB), mRNA.
7048	TGFBR2	*Homo sapiens* transforming growth factor, beta receptor II (70/80 kDa) (TGFBR2), transcript variant 2, mRNA.

SEQUENCE LISTING

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Asn Lys Asp Arg Phe Asn His Phe Ser Leu Thr Leu Asn Thr Asn His
        35                  40                  45

Gly His Ile Leu Val Asp Tyr Ser Lys Asn Leu Val Thr Glu Asp Val
    50                  55                  60

Met Arg Met Leu Val Asp Leu Ala Lys Ser Arg Gly Val Glu Ala Ala
65                  70                  75                  80

Arg Glu Arg Met Phe Asn Gly Glu Lys Ile Asn Tyr Thr Glu Gly Arg
                85                  90                  95

Ala Val Leu His Val Ala Leu Arg Asn Arg Ser Asn Thr Pro Ile Leu
            100                 105                 110

Val Asp Gly Lys Asp Val Met Pro Glu Val Asn Lys Val Leu Asp Lys
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Met Lys Ser Phe Cys Gln Arg Val Arg Ser Gly Asp Trp Lys Gly Tyr
    130                 135                 140

Thr Gly Lys Thr Ile Thr Asp Val Ile Asn Ile Gly Ile Gly Gly Ser
145                 150                 155                 160

Asp Leu Gly Pro Leu Met Val Thr Glu Ala Leu Lys Pro Tyr Ser Ser
                165                 170                 175

Gly Gly Pro Arg Val Trp Tyr Val Ser Asn Ile Asp Gly Thr His Ile
            180                 185                 190

Ala Lys Thr Leu Ala Gln Leu Asn Pro Glu Ser Ser Leu Phe Ile Ile
        195                 200                 205

Ala Ser Lys Thr Phe Thr Thr Gln Glu Thr Ile Thr Asn Ala Glu Thr
    210                 215                 220

Ala Lys Glu Trp Phe Leu Gln Ala Ala Lys Asp Pro Ser Ala Val Ala
225                 230                 235                 240

Lys His Phe Val Ala Leu Ser Thr Asn Thr Thr Lys Val Lys Glu Phe
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Gly Ile Asp Pro Gln Asn Met Phe Glu Phe Trp Asp Trp Val Gly Gly
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Arg Tyr Ser Leu Trp Ser Ala Ile Gly Leu Ser Ile Ala Leu His Val
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Gly Phe Asp Asn Phe Glu Gln Leu Leu Ser Gly Ala His Trp Met Asp
    290                 295                 300

Gln His Phe Arg Thr Thr Pro Leu Glu Lys Asn Ala Pro Val Leu Leu
305                 310                 315                 320

Ala Leu Leu Gly Ile Trp Tyr Ile Asn Cys Phe Gly Cys Glu Thr His
                325                 330                 335

Ala Met Leu Pro Tyr Asp Gln Tyr Leu His Arg Phe Ala Ala Tyr Phe
            340                 345                 350

Gln Gln Gly Asp Met Glu Ser Asn Gly Lys Tyr Ile Thr Lys Ser Gly
        355                 360                 365

Thr Arg Val Asp His Gln Thr Gly Pro Ile Val Trp Gly Glu Pro Gly
    370                 375                 380

Thr Asn Gly Gln His Ala Phe Tyr Gln Leu Ile His Gln Gly Thr Lys
385                 390                 395                 400

Met Ile Pro Cys Asp Phe Leu Ile Pro Val Gln Thr Gln His Pro Ile
                405                 410                 415

Arg Lys Gly Leu His His Lys Ile Leu Leu Ala Asn Phe Leu Ala Gln
            420                 425                 430

Thr Glu Ala Leu Met Arg Gly Lys Ser Thr Glu Glu Ala Arg Lys Glu
        435                 440                 445

Leu Gln Ala Ala Gly Lys Ser Pro Glu Asp Leu Glu Arg Leu Leu Pro
    450                 455                 460

His Lys Val Phe Glu Gly Asn Arg Pro Thr Asn Ser Ile Val Phe Thr
465                 470                 475                 480

Lys Leu Thr Pro Phe Met Leu Gly Ala Leu Val Ala Met Tyr Glu His
                485                 490                 495

Lys Ile Phe Val Gln Gly Ile Ile Trp Asp Ile Asn Ser Phe Asp Gln
            500                 505                 510

Trp Gly Val Glu Leu Gly Lys Gln Leu Ala Lys Lys Ile Glu Pro Glu
        515                 520                 525

Leu Asp Gly Ser Ala Gln Val Thr Ser His Asp Ala Ser Thr Asn Gly
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Leu Ile Asn Phe Ile Lys Gln Gln Arg Glu Ala Arg Val Gln
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What is claimed is:

1. A method for increasing migration or anchorage of a mesenchymal stromal cell (MSC) to a tumor comprising

(a) stimulating the MSC by in vitro pretreatment with a recombinant autocrine motility factor (rAMF) of SEQ ID NO:1, wherein the rAMF is capable of increasing migration or anchorage of a stimulated MSC, and

(b) administering the stimulated MSC of (a) to the tumor, wherein the MSC comprises a recombinant therapeutic agent,

wherein the vitro pretreatment comprises incubating the MSC with a medium comprising the rAMF followed by removal of the medium containing the rAMF.

2. A method for treating a subject with a tumor comprising

(a) stimulating a mesenchymal stromal cell (MSC) comprising a recombinant therapeutic agent by in vitro pretreatment with a recombinant autocrine motility factor (rAMF) of SEQ ID NO:1, wherein the rAMF is capable of increasing migration or anchorage of a stimulated MSC, and

(b) administering the stimulated MSC of (a) to the subject, wherein the in vitro pretreatment comprises incubating the MSC with a medium comprising the rAMF followed by removal of the medium containing the rAMF.

3. The method of claim **1**, wherein the tumor is a solid tumor.

4. The method of claim **1**, wherein the tumor is a cancer selected from the group consisting of a liver cancer, a colon cancer, a pancreatic cancer, a lung cancer, a gastrointestinal cancer, a kidney cancer, or a breast cancer.

5. The method of claim **1**, wherein the tumor is a carcinoma.

6. The method of claim **5**, wherein the carcinoma is hepatocellular carcinoma (HCC).

7. The method of claim **5**, wherein the carcinoma is colorectal carcinoma.

8. The method of claim **1**, wherein the tumor expresses endogenous AMF.

9. The method of claim **1**, wherein the increasing migration is two-fold greater than migration of the MSC without rAMF stimulation.

10. The method of claim **1**, wherein the source of the MSC is selected from the group consisting of bone marrow, adipose tissue, and umbilical cord.

11. The method of claim **10**, wherein the umbilical cord MSC is harvested from human umbilical cord perivascular tissue.

12. The method of claim **1**, wherein the recombinant therapeutic agent is a recombinant anti-tumor gene.

13. The method of claim **1**, wherein the recombinant therapeutic agent is an oncolytic virus.

14. The method of claim **13**, wherein the oncolytic virus is engineered to express a recombinant anti-tumor gene.

15. The method of claim **12**, wherein the recombinant anti-tumor gene is selected from the group consisting of an interferon, an interleukin, a chemokine, a suicide gene, and any combination thereof.

16. The method of claim **15**, wherein the anti-tumor gene is selected from the group consisting of interferon α, interferon ρ, interleukin 1, interleukin 12, CX3CL1, thymidine kinase, IL-12, IFN-gamma, TNF-alpha, or any combination thereof.

17. The method of claim **1**, wherein the MSC further comprises a recombinant AMF receptor.

18. The method of claim **2**, wherein the administration is systemic.

19. The method of claim **2**, wherein the administration is to an intra-hepatic artery.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 11,173,180 B2
APPLICATION NO. : 15/892680
DATED : November 16, 2021
INVENTOR(S) : Mazzolini et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page

Column 1, Item (73), in "Assignee", Line 1, delete "National" and insert -- Nacional --, therefor.

In the Claims

In Column 103, Claim 1, Line 3, delete "comprising" and insert -- comprising: --, therefor.

In Column 103, Claim 1, Line 11, delete "the" and insert -- the in --, therefor.

In Column 103, Claim 2, Line 15, delete "comprising" and insert -- comprising: --, therefor.

In Column 104, Claim 16, Line 25, delete "ρ," and insert -- β, --, therefor.

Signed and Sealed this
First Day of March, 2022

Drew Hirshfeld
Performing the Functions and Duties of the
Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office